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JULY--1956
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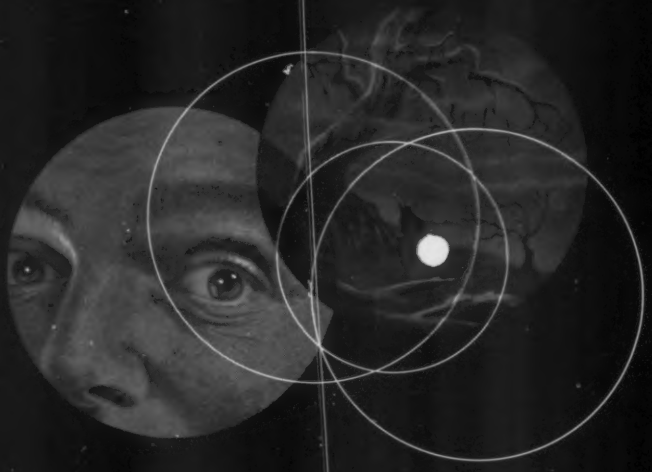

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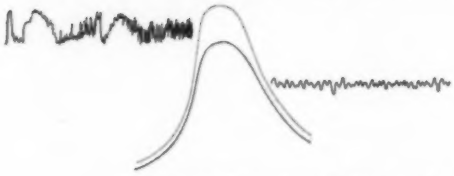

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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Volume 6 Neurology *Number 7*

Electroencephalographic Study of Insufficiency of the Basilar and Carotid Arteries in Man

John S. Meyer, M.D., Herbert Leiderman, M.D. and D. Denny-Brown, M.D.

CLINICAL OBSERVATIONS concerning syndromes due to occlusion of the internal carotid and basilar arteries[1] have led to the hypothesis that recurrent symptoms were due to hemodynamic crises resulting in failure of the cerebral collateral circulation in a compromised vascular territory, rather than due to a varying degree of "vasospasm" of the affected artery. In these clinical studies, falls in systolic blood pressure were found to be a frequent cause of failure or impairment of the collateral supply.

At necropsy there is frequently a large discrepancy between the severity of the clinical signs and the relative smallness and patchy distribution of infarction.[2,3] We, therefore, introduced a physiologic concept of widespread reversible ischemia associated with the hemodynamic crises of these states, determined by the variable efficiency of the extensive anastomoses of the circle of Willis.[1c] Arteriography in patients with occlusion of the major cerebral vessels and anatomic studies at necropsy have demonstrated the frequency of small arterial anastomoses providing the basis for additional adjustments in the collateral circulation beyond those provided by the circle of Willis.[1,5,6] In experimental studies in monkeys[4] we have been able to demonstrate slow, independent adjustments of cortical vessels to stress on their capacity as collaterals and the crucial role of systolic blood pressure in this phenomenon.

It was, therefore, to be anticipated that localized ischemia might be pro-

From the neurological unit, Boston City Hospital, and the department of neurology, Harvard Medical School, Boston.

With the technical assistance of Robert C. Struzziero.

These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and Harvard University, NR 115-401.

duced in patients with a severe degree of cerebrovascular insufficiency if their blood pressure was transiently lowered by postural change with the tilt-table. In order to study the lesser degrees of such changes and to avoid the production of severe crisis, the procedure was carried out during electroencephalographic recording and compared to brief carotid sinus compression in suitable patients. Carotid compression is a much more stressful test and is not without danger,[7] since it lowers the blood pressure by a depressor reflex in addition to occluding or embarrassing a major contributing vessel.

Many electroencephalographic studies have been made previously of the induction of syncope by postural changes[8–13] and of the effects of carotid compression, massage, and occlusion[14–16] but not in relation to cerebrovascular insufficiency due to disease of the carotid and basilar arteries.

Cerebrovascular insufficiency is defined in physiologic terms as a state of local or general cerebral blood flow that is unable to maintain the metabolic requirements of the brain during physiologic stresses. The state may be overt, leading to symptoms or signs during the physiologic stresses of normal life, or may be latent, requiring some extraordinary stress such as carotid occlusion or cardiac arrest before becoming manifest. This is a clinical condition, and to differentiate it from the effect of simple occlusion we would consider two or more episodes pointing to reversible changes in the same cerebral region to be desirable. It is obvious, however, that the condition may exist when only the first crisis has occurred and when only part of the disorder has been reversible. Until changes have again been induced referable to the same region, the nature of the condition is unproved. From such a definition it follows that a postural tilt is a physiologic test, whereas carotid compression introduces a stress beyond usual physiologic range.

When cerebrovascular insufficiency is localized, added stress commonly gives rise to transient focal neurologic signs (for example, transient hemiplegia, dysphasia, or dysarthria) due to ischemia in the distribution of the particular diseased vessel. The affected vessel is usually the basilar or one carotid artery or, more rarely, the main trunk of the middle cerebral artery. It has been described with bilateral carotid occlusion. It should be contrasted with the more generalized vascular insufficiency associated with transient failure of the systemic circulation, for example in aortic stenosis, Stokes-Adams syndrome, or postural syncope, even though this results in cerebral symptoms such as lightheadedness and dizziness followed by signs of syncope or generalized convulsions.

The present study indicates that, in the presence of localized cerebrovascular insufficiency, a temporary inadequacy may be demonstrated by its accompanying electroencephalographic changes when the cardiac output and collateral circulation are temporarily reduced by a change in posture or compression of one carotid artery in the neck. The occurrence of generalized effects is more common than hitherto suspected.

MATERIAL AND METHODS

In the neurological unit of Boston City Hospital, over 1,000 patients are studied electroencephalographically each year and of these 22 per cent suffer from cerebrovascular disease.

Tilt-table studies have been carried out on 130 individuals, of which the first 118 have been selected for inclusion in this study. All cases have been examined by one of the authors. In addition, data relating to the changes in blood pressure and pulse with postural tilt on 24 normal medical students with an average age of 23 were provided by the department of physiology. We have also made related clinical and electroencephalographic observations without the tilt-table on an additional 20 cases.

In the group suffering from cerebrovascular disease the clinical diagnosis was confirmed at necropsy in four and by arteriogram or direct surgical inspection of the vessel in an additional ten. In the remaining patients diagnosis was based on clinical signs and symptoms. None of the patients with basilar artery insufficiency has been examined at necropsy or had arteriography performed. The clinical history has, however, been sufficiently distinctive to allow more than presumptive diagnosis on clinical grounds.

For control purposes the electroencephalogram has been studied in relation to postural tilt to 70 degrees and carotid compression in seven young healthy males, in five young adults who have had surgical ligation or proved occlusion of a main cerebral vessel without recurrent symptoms, in 12 older patients without cerebrovascular disease, in two patients with arteriovenous malformations, in four patients with senile and presenile dementia, and in four patients with brain tumor or trauma. For purposes of comparison we have also studied 11 patients with syncope of various types.

All patients were thoroughly investigated clinically, including a detailed history, neurologic examination, and lumbar puncture. Clinical diagnosis of insufficiency of the internal carotid or basilar arteries was based on recurrent transient episodes of neurologic dysfunction in the distribution of one affected vessel as it has been generally understood.[1,3,17–19]

After a routine electroencephalogram was recorded, the tilt-table studies were carried out with regular readings of the brachial artery blood pressure. The electroencephalography cage was carefully shielded and the patients were grounded. The jack-box was mounted directly above the subject's head on the tilt-table and the leads were carefully protected from movement artefact caused by the tilt. In the control studies no change appeared in the electroencephalogram with postural tilt except rarely a reduction of alpha for a few seconds during the swing of the tilt-table. Bipolar recordings were found to be most satisfactory, although monopolar recordings were made in many patients. A minimum of eight scalp platinum needle electrodes were used in every patient, and in some patients more electrode placements were used. The eight electrodes were placed symmetrically in the usual frontal, central, temporal, and occipital positions. The electrocardiogram was also continuously recorded. The records were made with an eight channel Grass IIID electroencephalograph. At least four tilts to 70 degrees for two to five minutes were made in each patient unless a definite electroencephalographic focus appeared earlier. The first tilt was made slowly over a 25-second interval; later tilts were more rapid over an eight second interval. The patient was watched by two neurologists and any clinical observations were noted on the record. After the tilt-table study each carotid artery

was separately compressed in the neck for 30 seconds, unless electroencephalographic changes or symptoms appeared prior to this, when the pressure was immediately released. The carotid was compressed at the carotid sinus and the pressure was sufficient to occlude the vessel or reduce the caliber. A depressor reflex with a fall in blood pressure and slowing of the electrocardiogram frequently occurred. Some degree of hyperventilation accompanied the carotid compression in almost all subjects including the controls, but was more marked in patients with arteriosclerosis of the basilar and carotid arteries.

Hypotensive drugs were not used in this study because of the dangers of these agents in patients with cerebrovascular insufficiency.[1]

RESULTS — CLINICAL OBSERVATIONS

The use of the tilt-table was not found objectionable by any of the patients studied. In a few restless patients with severe vascular insufficiency, it was noted that they became quieter and more relaxed when postural tilting was begun. Postural tilt to 70 degrees produced no clinical symptoms or signs in any of the 13 patients with basilar artery insufficiency. In two of the 23 patients with occlusion of one carotid artery clinical signs and symptoms appeared. In both patients there was syncope of ten to 15 seconds duration, and in one with occlusion of the left carotid artery, a short focal seizure involving the right hand and arm appeared.

Carotid compression, however, produced signs and symptoms in a larger proportion of the cases studied. In only one case of basilar artery insufficiency did compression of the carotid artery produce an attack similar to those of which she had complained, but of the 23 cases of carotid artery insufficiency, compression of the remaining carotid caused unilateral or focal seizures in six and a generalized seizure in one. In the six cases in which a lateralized seizure occurred it was in the limbs of the side opposite to the compressed (intact) carotid in all instances except one.

It was apparent from the control study that the mean fall in systolic pressure with postural tilt increases with advancing age as shown in table 1. In the 63 year old group the mean fall in systolic pressure was almost twice that of the 28

TABLE 1

MEAN FALL IN BLOOD PRESSURE WITH 70° TILT—CONTROL GROUP

	Cases	*Mean Age*	*Mean B.P. (Horizontal)*	*Mean B.P. Fall (70° Tilt)*
Normal males	a) 24	23	124/78	8/5
	b) 7	28	121/75	12/3
Young patients with major vessel occluded (no recurrent symptoms)	5	36	128/86	13/3
Arteriovenous malformation	2	40	170/104	10/4
Brain tumor, trauma	4	42	136/ 82	22/9
Older patients without cerebrovascular disease	12	63	149/ 84	23/5
Dementia (senile, presenile)	4	64	155/ 88	10/4

year old group and more than twice that of the 24 year old group. In the young patients with ligation of a main cerebral vessel at surgery but without recurrent symptoms, the fall in systolic blood pressure with postural tilt was normal for that age group. It was also within normal limits in cases of arteriovenous malformation, senile and presenile dementias, brain tumor, and trauma.

In cases with cerebrovascular insufficiency due to disease of the carotid or basilar arteries, the fall in both systolic and diastolic blood pressure with postural tilt was found to be significantly increased (table 2). The blood pressure fall was greater in the carotid artery group than in the basilar artery group. In cases of disease of the middle, posterior, and anterior cerebral arteries, the fall in blood pressure with postural tilt was not significantly greater than with the controls, nor was the fall in blood pressure strikingly increased in those cases with a clinical diagnosis of diffuse cerebral arteriosclerosis or hypertensive vascular disease affecting small vessels with multiple cerebrovascular lesions.

In the control study there was no change of the electroencephalogram by postural tilt to 70 degrees in the young or elderly group or in those with miscellaneous neurologic conditions excluding degenerative vascular disease of the brain (table 3). This series included the senile and presenile dementias, brain tumor, trauma, and arteriovenous malformations. It is of special interest that in the group of young patients with occlusion of a large vessel but without recurrent symptoms and signs there was no change in the electroencephalogram with postural tilt.

With carotid compression, however, which is a much more stressful test, one of the young healthy controls developed electroencephalographic slowing ipsilateral to the compressed carotid artery and one of the young patients with a surgically ligated carotid artery developed diffuse slowing. It is of interest that the young healthy patient who developed slowing with compression of the right carotid artery was a 23 year old medical student who had had syncope on three occasions when his neck was constricted with a towel by playful schoolmates. He does not have carotid sinus sensitivity, and only the right carotid artery must be occluded to produce symptoms and electroencephalographic change. He also has postural

TABLE 2

MEAN FALL IN BLOOD PRESSURE WITH 70° TILT—CEREBROVASCULAR DISEASE

	Cases	*Mean Age*	*Mean B.P. (Horizontal)*	*Mean B.P. Fall (70° Tilt)*
Large Artery Disease				
Carotid insufficiency	23	63	170/ 93	46/23
Basilar insufficiency	13	72	165/ 91	39/15
Intermediate Artery Disease				
Anterior, middle and posterior cerebral arteries	14	57	138/ 76	25/ 2
*Small Artery Disease**				
Arteriosclerotic	18	70	150/ 87	27/11
Hypertensive	5	47	183/113	31/ 9

*Multiple small scattered infarcts

TABLE 3
EEG ABNORMALITIES WITH TILT AND CAROTID COMPRESSION—CONTROL GROUP

	Cases	*Resting Record*	*Tilt*	*Carotid Compression*
Normal males	7	0	0	1 (F)
Young patients with vessel occluded but without recurrent symptoms	5	3 (2F 1D)	0	1 (D)
Older patients without cerebrovascular disease	12	1 (D)	0	0
Miscellaneous group (tumor, trauma, presenile-senile dementias, arteriovenous malformations)	10	5 (1F 4D)	0	0

(F) Focal
(D) Diffuse or bilateral

dizziness without a severe fall in blood pressure. It is concluded that he has a congenital preponderance of the right carotid circulation, with a small or absent anterior communicating artery. There was no change in the older group with unilateral carotid compression.

In the group of patients with a diagnosis of insufficiency of the carotid artery, 21 out of 23 developed electroencephalographic changes with postural tilt to 70 degrees (table 4). In 11 the resting electroencephalogram was normal, and in ten an existing abnormality was accentuated. The resting abnormality, when present, was a slowing in the theta range over the temporal area in seven instances and was diffuse in three, but with a bitemporal preponderance. The slow activity usually appeared in bursts but in some instances was continuous.

With tilting to 70 degrees slowing in the theta and delta range appeared over the temporal region on the side of the occluded carotid artery in 15 and bitemporally in six and was of increased amplitude. Carotid compression on the side opposite to the affected vessel caused increased electroencephalographic abnor-

TABLE 4
EEG ABNORMALITIES WITH TILT AND CAROTID COMPRESSION—CEREBROVASCULAR DISEASE

	Cases	*Resting Record*	*Tilt*	*Carotid Compression*
Large Artery Disease				
Carotid insufficiency	23	10 (7F 3D)	21 (15F 6D)	23 (7F 16D)
Basilar insufficiency	13	4 (F)	9 (F)	7 (F)
Intermediate Artery Disease				
Anterior, middle and posterior cerebral arteries	14	8 (6F 2D)	7 (5F 2D)	5 (3F 2D)
Small Artery Disease				
Arteriosclerotic	18	2 (D)	4 (1F 3D)	4 (1F 3D)
Hypertensive	5	3 (D)	2 (D)	1 (D)

(F) Focal
(D) Diffuse or bilateral

mality in all 23, but was unilateral in only seven and diffuse in the remainder, with some poorly defined bitemporal preponderance.

In the group of patients with clinical evidence of basilar artery insufficiency four showed bioccipital slowing in the resting record, and with postural tilt nine showed an increase in this or the development of slowing in the occipital regions with some spread to the parietal and posterior temporal regions. With carotid compression seven showed a similar focal slowing in posterior regions of the head.

Of the 14 cases studied with diagnosis of occlusion of the anterior middle or posterior cerebral arteries, eight showed abnormalities of the resting electroencephalogram; in seven of these there was poorly defined accentuation of the abnormality by postural tilt and in five it was increased by carotid compression. These changes in the electroencephalogram with posture were never as striking in this group of patients as in those with basilar or carotid artery insufficiency.

Of the 22 patients with small cerebral infarcts from small vessel disease due to arteriosclerosis or hypertension, six showed an accentuation of the abnormality with tilt to 70 degrees and five with carotid compression. In only one instance did a focal abnormality appear.

REPRESENTATIVE CASES

Illustrations of the electroencephalograms from some of the patients, together with the following summaries of the case histories, are presented as typical examples.

Case 1. In figure 1 is shown the record of a 55 year old hypertensive woman with insufficiency of the left carotid artery. She developed mild right hemiparesis six years before examination, with episodic worsening over the

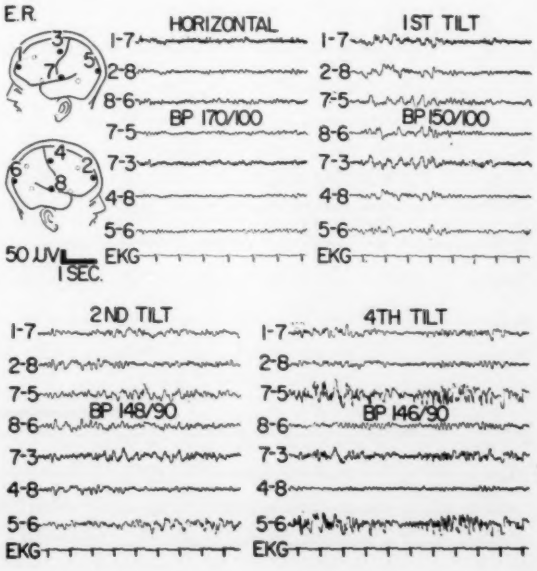

FIG. 1. *Case 1.* The effect of repeated tilts to 70 degrees is shown in a 55 year old hypertensive female with left carotid artery insufficiency and right-sided seizures. Note the spike activity in the left temporal region with the fourth tilt.

ensuing years and recurrent right-sided seizures approximately four times a year without further paralysis. Four years later she became blind in the left eye, and on examination she had diminished pulsation in the left carotid artery in the neck, occlusion of the central retinal artery, and a right spastic hemiparesis.

The resting electroencephalogram showed no abnormality, but with tilt to 70 degrees diffuse delta appeared in bursts as the blood pressure fell to 150/100. With repeated tilts the abnormality became paroxysmal and focal spikes appeared over the left temporal, parietal, and occipital regions. No clinical seizures were observed. Similar changes appeared with compression of the right carotid artery. This response is typical of carotid insufficiency when the test is not carried to the point of induction of clinical symptoms. It will be noted that with the first tilt only a generalized slowing was induced.

Case 2. The electroencephalogram of a 72 year old woman with left carotid artery insufficiency is illustrated in figure 2. She had suffered over a five year period from seven isolated episodes of transient acute confusion and agitation lasting one to five days. During these periods she was confused, dysphasic, and had a right-sided weakness, her speech was incoherent, and on three occasions the symptoms were ushered in by syncope. On each occasion these symptoms subsided with bed rest. On physical examination cardiac enlargement was noted with auricular fibrillation, increased tendon reflexes were present on the right, and the right plantar reflex was extensor. She showed spatial and temporal disorientation and jargon aphasia which resolved over a three day pe-

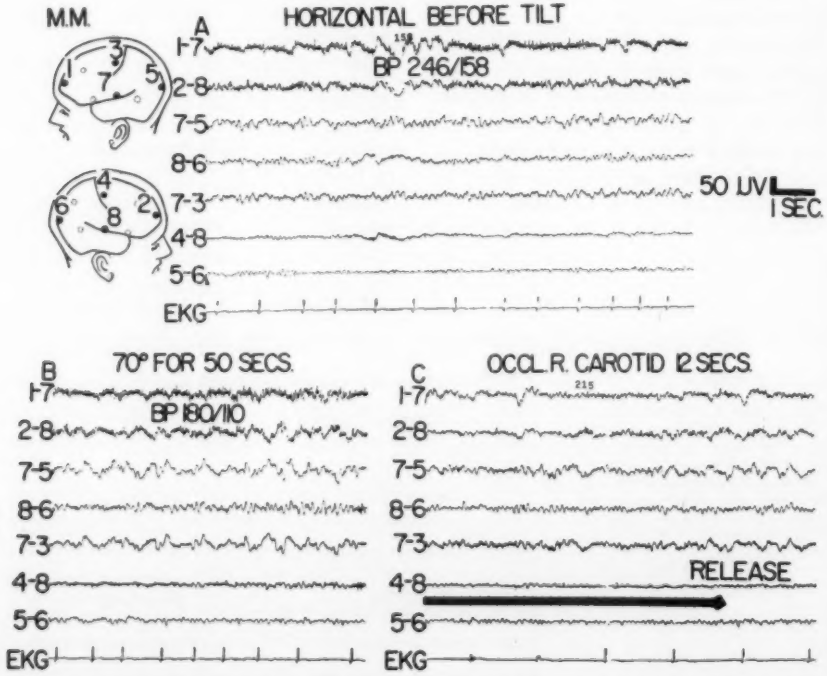

FIG. 2. *Case 2.* The effect of postural tilt to 70 degrees and carotid compression is shown in a 72 year old woman with left carotid artery insufficiency and episodic confusion. As the blood pressure falls focal delta activity appears in the left temporal region.

riod. Her electroencephalogram after recovery showed minimal bursts of 6 to 8 cps., slowing in the left temporal region when lying flat. Her blood pressure was 246/158 mm. Hg. When she was tilted to 70 degrees the blood pressure fell and continuous left temporal slowing in the theta and delta range appeared without symptoms. When the right carotid artery was compressed for 12 seconds the same left temporal slowing appeared and the electrocardiogram showed marked slowing.

Case 3. Figure 3 is the record of a 73 year old woman with insufficiency of the left internal carotid artery who was hospitalized because of step-wise progression over a four day period of confusion, disorientation, and right facial weakness, followed by dysphasia and a right-sided sensory loss one week later. The condition had improved with bed rest. The carotid pulse was diminished on the left. The resting electroencephalogram when the blood pressure was 160/80 showed some bitemporal slowing of moderate amplitude with left sided dominance. With tilt of 70 degrees the bitemporal slowing became increased in amplitude and decreased in frequency to the delta range. The left-sided dominance was still evident, and there had been some occipitoparietal spread on the left. When the right carotid artery was compressed for 11 seconds, high voltage slow waves appeared first over the ipsilateral frontotemporal region with bilateral spread, and a right frontal contraversive seizure with unconsciousness occurred. The electrocardiogram showed slowing and irregularity with carotid compression.

These three cases of carotid insufficiency illustrate the sensitivity of the Sylvian region on the side of the occluded or stenosed internal carotid artery to lowering of systolic blood pressure. The response is primarily in the form of delta waves appearing in the temporal lead. This ipsilateral preponderance was only relative, for with the more severe stimulus of occlusion of the opposite carotid artery the abnormality could be generalized and made transition to spike activity.

Case 4. Figure 4 is the record of a 78 year old man with diabetes mellitus and basilar artery insufficiency. He complained of transient spells of headache, vertigo, dimness of vision

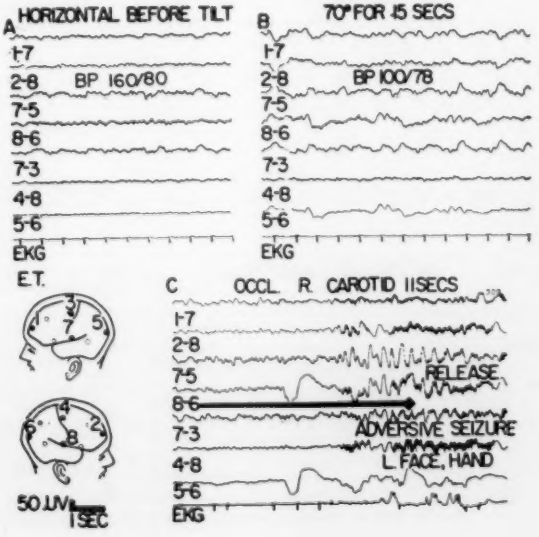

FIG. 3. *Case 3.* Samples of a continuous electroencephalographic record to show effect of postural tilt to 70 degrees and carotid compression in a 73 year old woman with insufficiency of the left internal carotid artery. Note the accentuation of the bitemporal slowing, with left temporal dominance.

or blindness, and trembling of the right hand. Physical examination showed mild ataxia, cerebellar tremor of the left hand, and bilateral extensor plantar reflexes.

The monopolar record shows that there was some bioccipital slowing in the theta range in the resting record. With tilt to 70 degrees his blood pressure fell from 120/80 to 90/60 mm. and bioccipital high voltage sharp waves and spikes appeared. He complained of no symptoms and the visual fields were full to confrontation at this time. As the blood pressure rose slowly to 118/80 the occipital abnormality decreased and slow waves appeared in the right parietal and temporal regions with some bilateral spread. This has been a characteristic finding in the presence of basilar artery insufficiency.

Case 5. The electroencephalogram of a 70 year old woman with basilar artery insufficiency is shown in figure 5. She entered the hospital after the sudden onset of semi-coma and right hemiparesis. She improved for five days and then had a second episode of dysarthria and ataxia now associated with a cerebellar tremor of the left hand. The eyes were deviated to the left, the tongue protruded to the right, and there was right spastic hemiplegia. She again improved with bed rest.

The resting electroencephalogram made after recovery showed alpha activity, with some eye movement artifact. With tilt to 70 degrees high voltage slowing and sharp waves appeared in both posterior temporal and occipital regions, with right-sided preponderance.

Case 6. Figure 6 is the record of a 63 year old colored woman with basilar artery thrombosis and insufficiency. She was admitted because of the sudden onset of vertigo, vomiting, tinnitus, right hemiparesis, and ataxia. She had

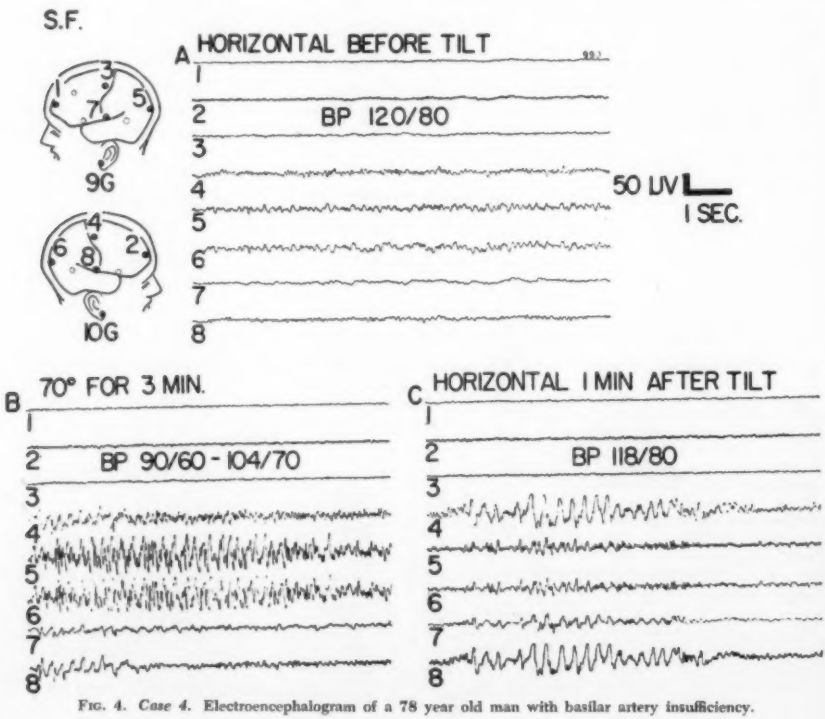

FIG. 4. *Case 4.* Electroencephalogram of a 78 year old man with basilar artery insufficiency.

had a similar transient episode six months before. On examination there were signs of arteriosclerotic heart disease and mild congestive failure. There were a left conjugate gaze palsy, left facial weakness, incoordination of all four extremities, bilateral spasticity, and ataxia. She made a remarkable improvement with bed rest.

Her resting electroencephalogram during the fourth week of convalescence was normal, but with postural tilt to 70 degrees high voltage delta appeared in the left posterior temporal and occipital regions without symptoms. A similar focal abnormality appeared with right or left carotid compression.

The unilaterality of the effect in this patient indicates an asymmetry in the carotid collaterals. From our necropsy studies in other cases we would predict either a very small or absent left posterior communicating artery (the most common anatomic variant) or some stenosis of the left internal carotid artery from arteriosclerosis. Her history and signs clearly indicated that the brainstem was the site of the most critical ischemia, and it was judged inadvisable to use arteriography to determine the exact nature of the defective collateral.

Case 7. Figure 7 is the electroencephalographic record of a 60 year old woman with insufficiency of the basilar artery, who entered the hospital because of five attacks of vertigo, dizziness, impaired vision, and syncope, with transient weakness of the left leg. She also noted weakness on arising suddenly. On physical examination there were impaired recent memory, extensor plantar responses bilaterally, and extinction hemianopia on the left. The resting electroencephalogram showed low voltage theta activity in the right temporooccipital region. With tilt to 70 degrees prolonged bursts of delta activity appeared in the right temporo-

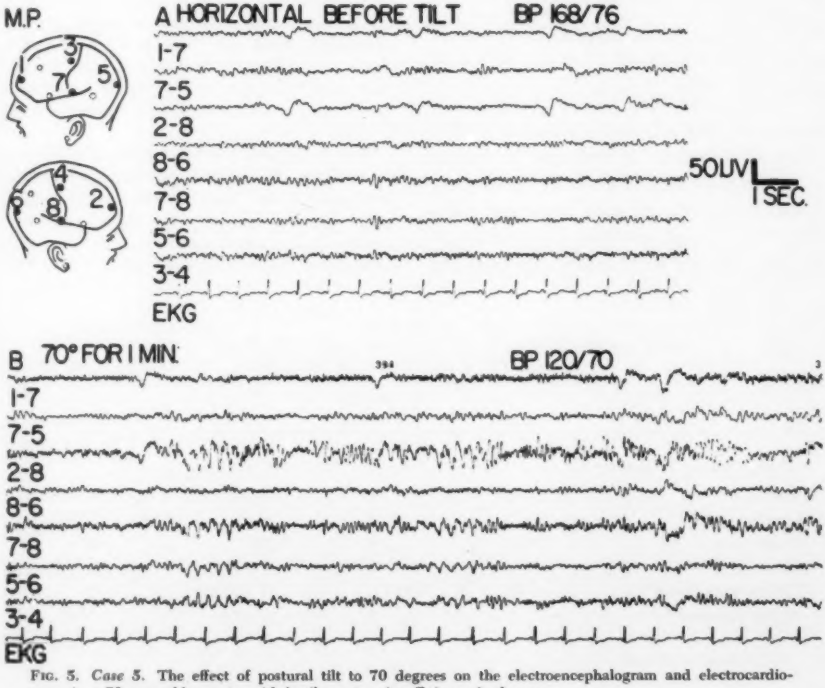

FIG. 5. *Case 5.* The effect of postural tilt to 70 degrees on the electroencephalogram and electrocardiogram in a 70 year old woman with basilar artery insufficiency is shown.

occipital region. Left carotid compression for 14 seconds in the horizontal position caused marked cardiac slowing, and high voltage delta activity appeared in both occipital regions, spread to the left and then the right temporal regions, and then became diffuse. The patient then said she had a typical attack with vertigo, a moving form appeared in her right visual field, and she raised her right hand. The attack ceased abruptly when the carotid artery was released.

This case also illustrates an asymmetric defect in the collateral circulation in basilar insufficiency. The clear-cut response in the right occipital region in this case indicates that the right posterior communicating artery is defective. Most of the cerebral circulation is provided by collaterals from the left carotid artery, and compression of this vessel caused a severe ischemia of both occipital regions with the production of symptoms. Compression of the right carotid produced bursts of right temporooccipital delta activity, but did not produce symptoms or the same degree of electroencephalographic change as compression of the left carotid artery.

Patients suffering primarily from syncope. Of the 11 cases referred with a clinical diagnosis of syncope of various types in whom clinical evidence of cerebrovascular abnormality was not obvious, five showed localized electroencephalographic patterns with postural tilt compatible with carotid artery insufficiency. This was particularly striking in those cases whose syncopal attacks had been precipitated by a sudden change in posture. In this subgroup two unquestionably had carotid artery insufficiency and one probably did (table 5).

Case 8. Figure 8 is the electroencephalogram of a 75 year old woman with myxedematous heart disease who was admitted because of recurrent syncope and stupor. She had gross physical signs of myxedema with cardiac decompensation, and her radioactive iodine uptake studies were too low to read. She was disoriented to time, place, and person and there was no palpable pulse of the left carotid artery. On sitting up the patient developed syncope. These symptoms were improved by thyroid therapy.

The electroencephalographic records were made on the first day of treatment and showed diffuse low voltage in the control run, but when the patient was tilted to 70 degrees the blood pressure fell and bursts of high voltage delta activity appeared in the left temporal region with a lesser degree of right temporal slowing.

Case 9. Figure 9 is the record of a 70 year old woman suffering from postural hypotension. She entered the hospital because of falling spells. She had syncope when she was elevated rapidly to the sitting position. She was also drowsy and showed impaired memory and lim-

TABLE 5

EEG ABNORMALITIES WITH TILT AND CAROTID COMPRESSION—GROUP WITH DIAGNOSIS OF SYNCOPE

	Cases	*Resting Record*	*Tilt*	*Carotid Compression*
Type of Syncope (Clinical)				
Postural	5	1 (F)	3 (2F 1D)*	1 (F)
Carotid sinus	2	0	0	1 (D)
Vasovagal	1	0	0	0
Blood loss	1	0	1 (F)*	1 (F)
"Myxedema heart"	1	0	1 (F)*	0
Aortic stenosis	1	0	1 (D)	N.E.

(F) Focal
(D) Diffuse or bilateral
N.E. Not examined
*EEG patterns compatible with carotid insufficiency.

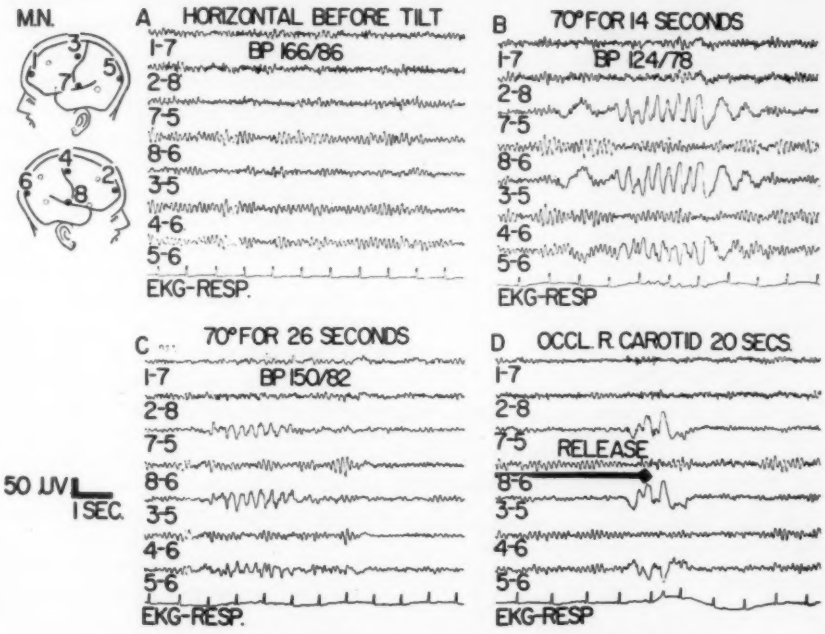

FIG. 6. *Case 6.* Electroencephalogram of a woman, age 63, with basilar artery insufficiency.

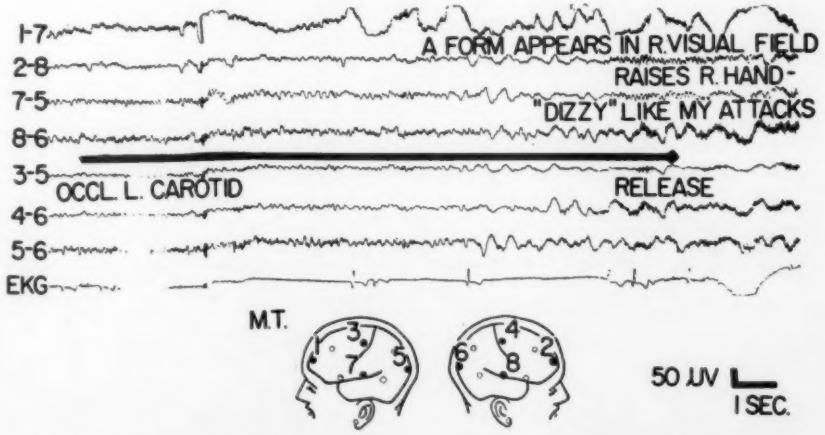

FIG. 7. *Case 7.* The effect of left carotid compression on the electroencephalogram in a 60 year old woman with insufficiency of the basilar artery.

ited attention span. Both plantar reflexes were extensor. There was evidence of diffuse arteriosclerosis.

The electroencephalogram showed temporal theta activity which was greatly increased by postural tilt, with slight right-sided preponderance. The bitemporal abnormality was also accentuated by left carotid compression, indicating the presence of right carotid artery insufficiency.

Case 10. Figure 10 is the electroencephalogram of a 72 year old woman who was referred because of severe aortic stenosis with recurrent syncope. She had cardiac murmurs characteristic of aortic stenosis, and the arterial pulse tracing showed delayed upstroke with each systole and an anacrotic notch.

Her routine electroencephalogram showed some left temporal slowing in the theta range occurring in bursts. With postural tilt to 70 degrees bitemporal and diffuse high voltage slowing appeared, associated with the marked fall in systolic and diastolic blood pressure. This illustrates the effect of general circulatory insufficiency without obvious cerebrovascular factor.

DISCUSSION

The results of this study indicate that the electroencephalogram is a sensitive indicator of mild regional ischemia in patients with recurrent cerebrovascular symptoms due to advanced arteriosclerosis when cerebrovascular insufficiency is stressed by postural change with the tilt-table or carotid compression. The latter procedure is a more rigorous and less specific test because, in addition to occluding a major cerebral vessel, there is general reduction of blood pressure. The electroencephalographic changes consist of a decrease in frequency and an increase in amplitude in the distribution of the affected vessel. Thus, when episodes indicating insufficiency of the contribution of the left internal carotid artery to the circle of Willis have been present, lowering the blood pressure by postural tilt evoked electroencephalographic changes more localized to the left temporooccipital region (cases 1, 2, and 3). Lesser changes in the right hemisphere are interpreted to indicate that the contralateral internal carotid supply, compromised by its need to contribute

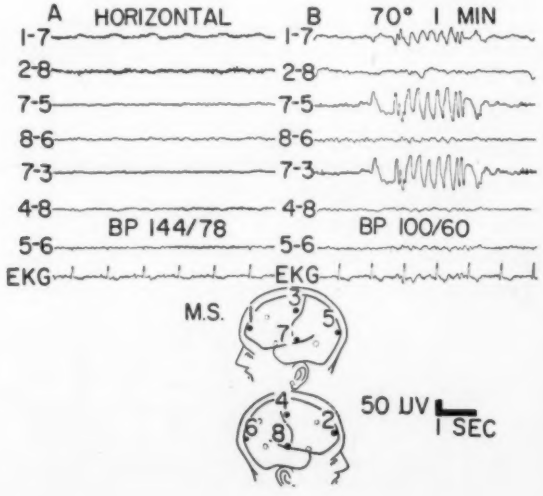

FIG. 8. *Case 8.* Electroencephalogram of a 75 year old woman with myxedema, postural syncope, and occlusion of the left carotid artery.

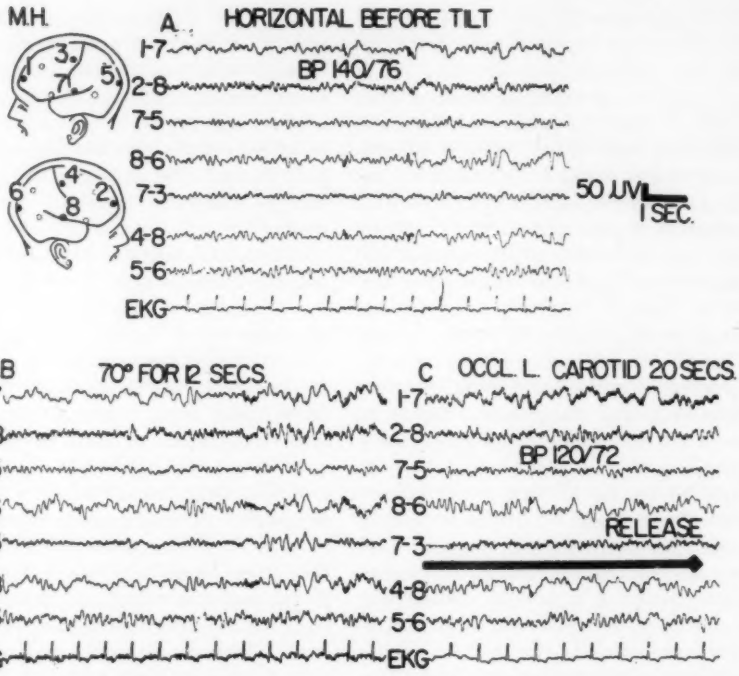

FIG. 9. *Case 9.* Electroencephalogram of a 70 year old woman with postural syncope and right carotid artery insufficiency.

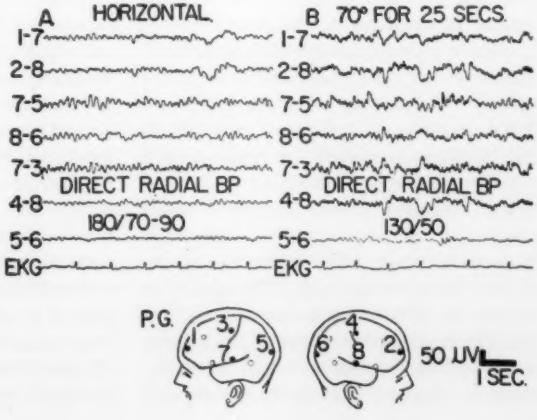

FIG. 10. *Case 10.* Record from a 72 year old patient with severe aortic stenosis and recurrent syncopal episodes.

to the defective hemisphere as well as its own, is also sensitized to some degree to falls in systolic pressure. The test of occlusion of the contralateral carotid, as might be expected, adds additional emphasis on both effects, though the primary change is still in the ischemic area. If either test is carried to the point of induction of convulsive activity, spiking first appears in the region of most abrupt fall in blood flow, usually the side of the lesion with tilting (case 1), but often on the side of the better carotid when that vessel is compressed (case 3).

Similarly, in the presence of recurrent signs of basilar insufficiency, tilting induces the same type of electroencephalographic change in the general regions supplied by the posterior cerebral arteries (cases 4 and 5). It was commonly found, however, that the resulting electroencephalographic changes were asymmetric (cases 6 and 7), a finding that is consistent with the well known asymmetric variations in size of the posterior communicating arteries and of the posterior cerebral trunks. An arrangement of a small or absent posterior communicating artery on one side is a common vascular anomaly estimated to be present in 12 per cent of autopsies.[20]

The symptomatology of carotid and basilar insufficiency reflects the localized effects of episodes of inadequacy related to severe degrees of ischemia in the territory supplied by the affected vessel. The electroencephalogram will record changes accompanying a lesser degree of the same pattern, which can thus be studied without the risk of inducing ischemic necrosis. The ability to reproduce both the symptoms as well as the electroencephalographic changes in some selected patients (for example, case 7) showed that both are aspects of the same ischemic process. The sensitivity of the electroencephalographic changes to provocation by an uncomplicated drop in systolic blood pressure reinforces our original conclusion that this is an important, possibly the most important, factor in the causation of cerebral hemodynamic crises in such patients.[1,4]

The more sensitive electroencephalographic changes also demonstrate that the hemodynamic disturbance in cases of carotid and basilar insufficiency is only relatively localized to the territory of the artery that is primarily stenosed or occluded. None of the cases reported in detail here has yet come to necropsy, so it is not yet possible in these cases to define with accuracy whether stenosis or complete occlusion was present. However, in two recent cases not included in this group, with a transient left hemiplegia and diminished pulsation of the right carotid artery in the neck, electroencephalograms demonstrated marked accentuation of right temporal slowing with tilt-table or compression of the left carotid artery. Right carotid arteriography demonstrated in both a severely stenosed (but not occluded) proximal portion of the internal carotid artery on the right. In the essentials of a hemodynamic crisis this question is not important, for it seems clear that the situation of an occluded vessel with relatively good collaterals is essentially the same as that of a stenosed vessel with poor collaterals. Since the material reported here is drawn from cases of arteriosclerotic disease late in life, it is likely that collateral circulation is impaired to some degree in all cases. There is some evidence that the presence of the syndrome of insufficiency is itself due to impairment of collateral circulation, whether

by anomalous smallness of communicating arteries or by arteriosclerotic damage to previously competent anastomoses. It is, therefore, not surprising that the hemodynamic crisis induced by postural tilt, and particularly by carotid compression, should induce some generalized electroencephalographic change as well as a focal disturbance. The cerebrovascular resistance in vessels that are serving as collaterals to a compromised network as well as supplying their own territory must be lowered. The effect of a fall in systolic pressure will be correspondingly exaggerated. In this way the hemodynamic crisis can affect both hemispheres when any one large tributary to the circle of Willis is compromised. Some more generalized effect of the hemodynamic crisis is commonly seen in the electroencephalogram. The prominence of attacks of syncope in the histories of some patients is possible evidence of such diffuse effect.

SYNCOPE DUE TO BASILAR AND CAROTID OCCLUSION

Examination of a series of patients in whom the presenting disability had been attacks of syncope provided unexpected confirmation of the importance of diffuse failure of collaterals in the production of symptoms. In five of 11 cases of syncope without obvious evidence of cerebrovascular abnormality, unmistakable electroencephalographic signs of relative carotid insufficiency were found. In two of these patients detailed neurologic examination and palpation of the carotid arteries confirmed the diagnosis of carotid insufficiency. Asymmetric but diffuse high voltage slow waves were found, identical with those seen in other cases of more obvious carotid insufficiency when dizziness and syncope had been associated with recurrent paralytic symptoms. The reason for accentuation of symptoms of general failure in such cases must await detailed correlation of pathologic and clinical findings. It is already apparent, however, that the age of the patient at the time of onset of occlusion of a major vessel is of paramount importance to the efficiency of the collateral circulation, and therefore probably determines the pattern of symptomatic failure when such collaterals become impaired by arteriosclerosis.

In reviewing the literature on reported cases of the cephalic type of carotid sinus sensitivity, we are inclined to agree with Webster and co-workers[27] that carotid artery insufficiency may have played an important role in many such cases. We are of the opinion that many if not all of the patients collected by Askey[7] who developed hemiplegia following carotid compression had advanced carotid artery insufficiency. Such experiences warn that digital compression should not be prolonged without electroencephalographic monitoring when there is a history of recurrent episodes of hemiparesis and syncope.

Our study indicates that a severe degree of cerebrovascular insufficiency must be present before the postural changes appear in the electroencephalogram. Thus, in five young patients with known ligations of either one vertebral, carotid, or middle cerebral artery, there was no accentuation of electroencephalographic abnormality with postural changes, presumably because of the excellent collateral circulation in young individuals and the absence of severe postural changes in blood pressure (table 1). Such factors must be considered in evaluating any patient prior to surgical

ligation of a carotid artery rather than depending on any electroencephalographic test alone.[15]

The striking liability of elderly patients with disease of the carotid and basilar arteries to marked falls in blood pressure with change in posture was an incidental but important observation (table 2). We have also confirmed the frequent association of hypersensitivity of the carotid sinus reflex with disease of the carotid arteries that has been noted by others.[21–23] It is our view that the similar liability of patients with arteriosclerosis of the carotid and basilar arteries to postural hypotension is due to involvement of the carotid and aortic baroreceptors and to the rigidity of all large vessels in this disease. This concept is further supported by our observation that there is an increased hyperventilation response in these patients with carotid compression (figure 7). This maneuver causes hypoxia of the carotid body receptors which results in stimulation of the respiratory center via a reflex mechanism.[25]

EFFECT OF INFARCTION ON SIGNS OF INSUFFICIENCY

The presence of the syndrome of cerebrovascular insufficiency implies a discrepancy between supply of arterial blood and tissue demand for oxygen. Our experimental studies with the polarographic technic in monkey cortex[4,35] demonstrates the high oxygen consumption and small oxygen reservoir of cerebral tissue. A cerebral infarct, on the contrary, has a minimal oxygen consumption.[36] It follows that once infarction has occurred in an area subject to insufficiency, the degree of insufficiency is partially compensated both by lessening of extent of the capillary net and by the fall in oxygen demand. Indeed the infarct itself begins to act as an oxygen reservoir, for under conditions of ischemia or anoxia it slowly loses oxygen to surrounding tissue.[36] When carotid insufficiency has led to extensive infarction, it is to be expected that the changes induced by postural tilt will be smaller and less localized than in comparable cases without infarction. This has in fact been a prominent feature in the series of cases reported here. It will be noted, for example, that the changes in cases 4, 6, and 8, with few or no signs of infarction, are particularly clear cut and of high voltage. Eighty-three per cent of the patients with symptoms of insufficiency showed a positive electroencephalographic response to postural tilt. Analysis of the six cases that did not show response showed that four of them had signs of large infarctions in the distribution of the insufficient vessel. In patients in whom extensive infarction ultimately led to autopsy, the effect of postural change on the electroencephalogram usually had been small. It is likely that continued insufficiency at the border of the lesion is largely responsible for the remaining electroencephalographic changes in such patients, but it has not been possible to exclude other factors. For this reason the electroencephalographic changes have been more readily studied in cases with minimal cerebral damage.

If reduction of systolic blood pressure is the principal factor in the production of symptoms in patients suffering from the syndrome of cerebrovascular insufficiency, it might be expected that postural tilt would regularly reproduce the symptoms. In this series of patients selected at random with a history of such insufficiency the symptoms were repro-

duced in only 5 per cent. Had the test been made more severe by the use of hypotensive drugs, we have no doubt that symptoms would have been reproduced more regularly, but this would be a dangerous and unphysiologic test.

The more generalized electroencephalographic changes seen in many of our cases as a result of stress suggest that large vessels acting as collaterals for adjacent areas of ischemia had now become prone to decompensation themselves.

MECHANISM OF TRANSIENT CEREBRAL SYMPTOMS

In most of our cases the electroencephalic response to the tilt-table has revealed the defect by its induction by moderate falls in blood pressure. We, therefore, conclude that reduction of systolic blood pressure is an important factor in the production of symptoms.

Examples of the importance of falls in systolic blood pressure in producing symptoms are commonly seen in the clinic. For example, a 56 year old woman had partial, intermittent carotid closure with a Selverstone clamp for treatment of saccular aneurysm of the left internal carotid artery. On two occasions the clamp was released because of transient neurologic signs of focal cerebral ischemia (right hemiparesis, dysphasia). Eventually the clamp was closed without further symptoms. After closure of the vessel, postural tilt demonstrated transient electroencephalographic slowing in the distribution of the occluded vessel.

We have further clinical observations on other patients with transient neurologic signs in whom, by chance of nature, the cardiac output was transiently reduced. For example, a 59 year old hypertensive male was admitted with Stokes-Adams syndrome, recurrent syncope, convulsions, and left hemiplegia. The electrocardiogram showed periodic heart block. On two occasions during the periods of intermittent heart block, he developed a transient left hemiplegia. At necropsy, examination of the brain revealed stenosis of the parasellar portion of the right internal carotid artery and a small posterior communicating artery on the right side. The heart showed coronary arteriosclerosis.

Another case in point was that of a 73 year old male who developed occlusion of the right middle cerebral artery with a left hemiparesis and cortical sensory loss. His blood pressure was charted every two hours for 14 days. On the fifth hospital day he developed transient auricular fibrillation and his blood pressure fell from 140/90 to 90/60 for 12 hours. During this period he had ten left-sided, unconscious, controversive seizures of two to three minutes' duration without status epilepticus. He was digitalized and his blood pressure rose to 140/90; there were no further seizures and the hemiparesis was improving on the fourteenth day when he succumbed to a pulmonary embolus. Others have shown by simultaneous electroencephalographic and electrocardiographic traces during complete heart block that asymmetric electroencephalographic abnormalities may arise,[30] indicating localized cerebrovascular insufficiency.

A striking case showed that these transient symptoms are due to local failure of the cerebral circulation. An 80 year old man had a history of intermittent syncope, transient left hemiparesis, monocular blindness, and occipital headache. He had an enlarged heart with slow auricular fibrillation. Neurologic

examination showed a mild, spastic, left hemiparesis and absence of reaction to light in the right eye, with preservation of the consensual response. The right fundus was pale. If he sat up segmentation of arterial blood and slow circulation in the veins became visible. Light pressure on the right eye arrested the retinal circulation. The left eye was normal. Pressure on the left carotid produced arrest of the circulation in the right eye and segmentation of the retinal veins of the left eye, with pulsatile flow in the central artery of the retina. When the carotid pressure was released the segmented red blood cells closed together and the circulation was resumed in a pulsatile manner. Tilting up the foot of the bed restored normal circulation to both fundi. Tilting up the head of the bed to sitting position caused a return of segmentation in the right retinal veins and pallor of the disk. Normal circulation was again restored in the horizontal position.

Foley,[31] in a pathologic analysis of a large number of autopsied cases of cerebrovascular disease in the elderly at this hospital, emphasized the prominence of extracerebral causes of localized cerebrovascular failure. Myocardial infarction, coronary insufficiency, and angina pectoris were found to be commonly associated with the appearance of localized cerebral infarction.

Lennox and his associates[28] showed that, in syncope associated with a critical fall in blood pressure, there is a delay of six to eight seconds after the heart stops beating before consciousness is lost and the electroencephalogram shows slow activity. At this time the blood leaving the brain was less than 24 per cent saturated with oxygen. Eletroencephalographic changes in the patients studied in our own group frequently appeared within eight to 15 seconds of change in posture or carotid compression (figures 2, 3, 6, 7, and 9). We have shown experimentally that the electroencephalographic change accompanying carotid occlusion is related to hypoxia of the cortical tissue.[4] In these studies it was also shown that the collateral circulation following occlusion of a cerebral vessel fails when the systemic blood pressure falls.[4] We have recently confirmed these findings in man using similar technics in the neurosurgical operating room. Occlusion of the carotid artery causes a transient cortical hypoxia and fall in cortical temperature in the distribution of its supply. A fall in blood pressure in the presence of occlusion of the carotid artery results in a fall of cortical oxygen availability, which is greatest in the distribution of the occluded vessel.[29]

Recent studies of cerebral blood flow in man have shown, as we found in animals, that there is a critical blood pressure necessary to maintain adequate cerebral circulation. In normal individuals this critical blood pressure is stated to be 55 to 60 mm. Hg, but in patients with relatively fixed cerebrovascular resistance (malignant hypertension) the critical blood pressure is considerably higher.[32,33] If local cerebrovascular insufficiency was present in the latter group of patients, a fall in blood pressure might be assumed to be disastrous. Using the same technic of hypotensive drugs combined with the tilt-table, gross electroencephalographic changes may be precipitated in patients without cerebrovascular disease by lowering the blood pressure below the critical level. In subjects with hypertension the electroencephalographic changes appeared at

a relatively higher level of blood pressure.[34]

MECHANISMS OF TRANSIENT ISCHEMIC NEURONAL PARALYSIS

We have shown experimentally that the early consequences of cerebral ischemia are due to local hypoxic damage to neurons.[4] Anoxia results in two reversible degrees of nerve cell injury. The first change is reflected in the electroencephalogram as a slowing and increase in potentials and occurs after about eight seconds of anoxia, while the second change is the injury potential or S.P. shift which occurs after two to four minutes, is usually associated with cessation or suppression of local electroencephalographic activity, and is reversible if anoxia is not prolnged beyond three and a half minutes.[35,37,38] However, if a slight flow of blood is present and hypoxia is not complete, then cerebrovascular occlusion can be tolerated for longer periods of time with recovery. The length of time will depend on the collateral circulation and hence on the systemic blood pressure. Thus, in experimental occlusion of the middle cerebral artery the degree of infarction will depend on the maintenance of blood pressure. In the presence of a well sustained blood pressure, the middle cerebral artery may be occluded in the monkey for as long as 15 minutes without infarction.[39,40] Indeed Gänshirt and associates have demonstrated that, when the electroencephalogram is rendered isoelectric by transient total cerebral ischemia, the basal metabolic requirement to maintain the viability of the damaged nerve cells is 20 per cent of that for normal functional activity.[38]

These physiologic data in animals conform with our own observations in man with cerebral infarction, where serial electroencephalographic records frequently show a flattening of brain waves over the local area of brain injury in the paralytic stage, usually followed by resolution of the electroencephalographic abnormality before functional recovery.

THERAPEUTIC CONSIDERATIONS

Interest in the therapy of basilar and carotid artery syndromes has been stimulated by a wider understanding of their pathogenesis. Maintenance of blood pressure is of primary importance[1] and hypotensive drugs should be avoided. Experimental studies indicated that oxygen is of value if local ischemia is severe.[4,35] In view of the demonstration of postural hypotension as a complicating factor in these disorders, chlorpromazine and the rauwolfia group of drugs should be avoided since they tend to increase postural hypotension. We find tight abdominal binders and elastic stockings useful in avoiding severe falls in blood pressure with change of posture and the ensuing symptoms of cerebral ischemia. Ephedrine and atropine administration minimizes the carotid sinus depressor mechanism which is hyperactive in many of these patients and reduces postural hypotension. In carefully selected cases we have had excellent results by surgical reconstruction of the stenosed or obstructed carotid artery.[41] Recently promising results have been reported with anticoagulants,[17–19] and we have also found this beneficial in a limited series. We have found the method of study reported here helpful in evaluating treatment of these patients and in a better understanding of their complaints.

SUMMARY

Thirty-six patients with recurrent cerebrovascular symptoms due to severe insufficiency of the internal carotid and basilar arteries have been studied in terms of the electroencephalogram, electrocardiogram, blood pressure, and clinical manifestations as the blood pressure was lowered by repeated postural tilting (tilt-table) and carotid compression. Such falls in blood pressure may be demonstrated to give rise to changes in the electroencephalogram consistent with transient focal cerebral ischemia. In general, patients with carotid artery insufficiency develop electroencephalographic slowing over the Sylvian area and patients with basilar artery insufficiency develop slowing over regions supplied by the posterior cerebral arteries. Electroencephalographic changes did not appear in a control group including patients with senile and presenile dementias. In addition, 11 patients with an admission diagnosis of syncope of various types were similarly studied, of whom five showed changes compatible with carotid artery insufficiency. The combination of cerebrovascular disease and heart disease results in serious liability to postural ischemia of the brain.

These studies show that insufficiency of the internal carotid or basilar arteries may give rise to generalized disturbance associated with syncope, mental confusion, episodic dementia, and seizures, as well as focal signs. The fall in cerebrovascular resistance of the vessels of collateral supply is the probable cause of such generalization of effect. On the contrary, when areas of infarction occur in the compromised region, the lessening of the local tissue metabolic rate and the reduction of the vascular bed tend to lessen the degree of insufficiency. The fall in blood pressure with postural tilting was found to be significantly greater in patients with carotid or basilar artery insufficiency than in a control group without cerebrovascular disease.

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Congenital Obliteration of the Anterior Portion of the Lateral Ventricle

F. Miles Skultety, M.D. and Robert G. Hardy, M.D.

THIS PAPER records a case of apparent maldevelopment of the right lateral ventricle and obliteration of the right foramen of Monro. Our review of the literature has failed to reveal a similar instance.

REPORT OF CASE

A white female infant was the product of an apparently normal pregnancy. There was no history of intercurrent infection or other complications. Spontaneous labor and delivery occurred on December 13, 1953, approximately one month prior to the expected date of confinement. The baby weighed 2,055 gm. at birth, was reported to have appeared normal, and required no resuscitation. The head circumference was 32 cm.

The infant was given routine premature care in the nursery and did moderately well, except that during the first postnatal month the circumference of the head increased 4 cm. Ventriculography and dye transference tests on three separate occasions disclosed similar results: 1) a large cavity was demonstrated in the posterior two-thirds of the right hemisphere, apparently unconnected with the third and left lateral ventricles; and 2) dye instilled in this cavity was not recovered in the spinal fluid. The left lateral ventricle did not fill adequately.

First operation, February 10, 1954: A right parietal craniotomy was performed when the baby was 59 days old. Upon incising the cortex to a depth of 5 mm., a smoothly-lined (seemingly ependymal) cavity containing approximately 150 cc. of clear fluid was entered. The choroid plexus was identified on the inferomedial wall of the cavity. It arose medially from the region of a bluish, vascular-appearing mass of tissue approximately 1.5 cm. in diameter and ran laterally and anteriorly onto the medial wall of an inferolateral extension of the cavity. The latter appeared to represent a dilated temporal horn. Medially, no foramen of Munro was demonstrated. Another small, smoothly-lined cyst, approximately 15 cc. in volume, was located just anterior to the anteromedial extent of the larger cavity. A communication existed between the small and large cavities via an opening 0.5 mm. in diameter just dorsal to the previously described area from which the choroid plexus arose. No definitive surgical procedure was carried out.

The postoperative course was uneventful and the infant did well following discharge from the hospital, gaining weight and appearing to develop at a pace commensurate with age. The head circumference (39 cm.) remained essentially unchanged during the first two postoperative months.

The baby was readmitted to the hospital five months after operation because of inordinate enlargement of the head noted during the third postoperative month. In other respects the infant had done well. The head circumference on admission was 45.5 cm. The baby appeared well nourished and alert. She moved all extremities in well integrated patterns, but could not sit up without support. A pneumoencephalogram revealed a normal-appearing third ventricle and a minimally dilated left lateral ventricle. No air was visualized in the right lateral ventricle. The third and left lateral ventricles were shifted to the left, suggesting a mass in the posterior portion of the right hemisphere.

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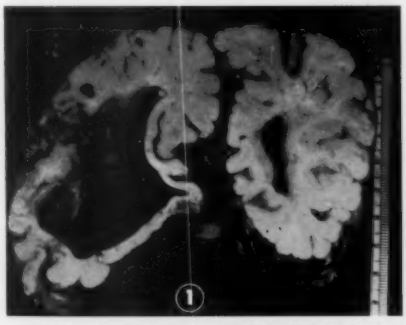
Second operation, July 15, 1954: The posterior portion of the right hemisphere was reexplored and the large cavity was again entered. An estimated 300 cc. of clear fluid was evacuated. Esssentially the same findings presented as were disclosed at the first operation. The frontal horn and the foramen of Monro appeared obliterated so that the remaining portion of the body and the posterior and temporal horns of the lateral ventricle constituted a cystic mass. In an effort to establish drainage into the subarachnoid space via the choroid fissure, as described by Hyndman,[1] the choroid plexus was avulsed.

The patient seemed to do well immediately after operation but expired suddenly 12 hours later.

Postmortem examination revealed the presence of several cubic centimeters of gastric contents in the upper trachea. The lungs were clear except for slight congestion of their posterior aspects. The right cerebral hemisphere appeared slightly larger than the left. The convolutions were flattened and the gyri over the right temporal and posterior parietal regions appeared abnormally small. A thin layer of blood covered the mammillary bodies and the inferior surfaces of the pons and medulla. "Coronal" sections, made by the prosector, were sliced in such a way that the midbrain was cut obliquely, that is, caudally from above downward. Gross examination revealed a normal-appearing third ventricle, aqueduct, and fourth ventricle. The left lateral ventricle was slightly dilated. The cerebellum and brainstem appeared grossly normal. In the right hemisphere, no ventricle was discernible back as far as the level of the mamillary bodies. However, a small, apparently isolated cavity, estimated to be about 15 cc. in volume, was seen just anterior to the large cavity as described above. Behind the level of the mammillary bodies a large, dilated ventricular cavity was present on the right with markedly thin overlying cerebral tissue, approximately 0.5 cm. in thickness in most places, but ranging up to 3 cm. in some regions (figure 1).

A coronal section made just behind the rostral limit of the septum pellucidum demonstrated clearly the two leaves of the septum slightly separated by the cavum septi pellucidi and a slightly dilated ventricular cavity on the left, without a corresponding cavity on the right (figure 2).

The failure to demonstrate at operation a connection between the dilated posterior portion of the right lateral ventricle and the third ventricle was confirmed at necropsy. A foramen of Monro was demonstrable on the left but no counterpart was seen on the right, nor was any gross counterpart of a ventricle apparent (figure 3). In a section through the caudal margin of the foramen of Monro, the choroid plexus was visible in the left lateral and third ventricles. No counterpart of choroid plexus was seen on the right. The fornices, in a poor state of preservation, were seen above the third ventricle. Their more ventral portions were seen



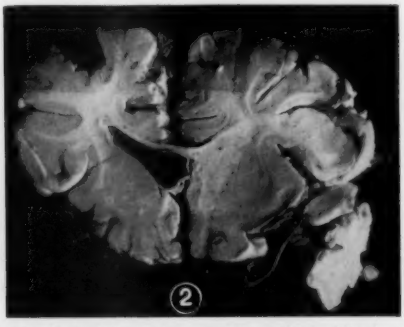


FIG. 1. A coronal section of the cerebral hemispheres at the level of the atrium revealing markedly dilated right lateral ventricle at this level.

FIG. 2. A coronal section just behind the rostral limit of the septum pellucidum. The leaves of the septum are separated, demonstrating the cavum septi pellucidi. There is a slightly dilated ventricular cavity on the left with no corresponding cavity on the right.

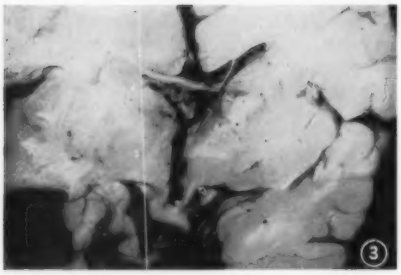


FIG. 3. A coronal section just anterior to the region of the foramen of Monro. A bristle passes through the left foramen of Monro. On the right side no corresponding foramen or gross counterpart of a ventricle is seen. (The section is cut somewhat obliquely, trending caudally from left to right.)

near the levels of entry into the mammillary region. A large amount of thalamic tissue was present on the right, occupying the region ordinarily occupied by the lateral ventricle (figure 4).

Microscopic hematoxylin and eosin stains revealed ependymal cells arranged as cords, small rosettes, and segmented tubules dorsolateral to the right thalamus in the region where parts II and III of the lateral ventricle ordinarily would be found (figure 5).

Microscopic examination of a section of the frontal lobe normally occupied by the frontal horn of the lateral ventricle, part I, demonstrated ependymal cells in a thin line dorsolateral to the head of the caudate nucleus. The configuration was similar to that described above in the region of the thalamus (figure 6).

The cellular detail of the head of the right caudate nucleus in the region of the absent ventricle was compared with the caudate head from the corresponding region of a child 49 days older without neurologic deficit who died of pulmonary edema secondary to heart failure. The sections revealed perceptibly larger nuclei in the case under present inquiry than in the "control." Thus, random measurements of the nuclei in the former ranged from 5 to 10 micra (average 7.6 u), while those in the "control" ranged from 5 to 8 micra (average 6.2 u). Random counts of cells in fields of corresponding size (25,600 square micra) revealed ten to 12 cells in each case. This indicates that the increase in size of the caudate head was characterized by an hypertrophy of cells rather than hyperplasia.

DISCUSSION

This case represents an instance of obliteration of the anterior portion of the right lateral ventricle and foramen of Monro, associated with a unilateral "obstructive" hydrocephalus of the remaining portion of the lateral ventricle. A question that merits immediate inquiry has to do with the etiologic and pathogenic factors responsible for such obliteration. The principal alternatives in this case appear to rest with 1) developmental ("dysplastic") events and 2) the response of previously healthy tissues to an inflammatory agent (infectious and/or toxic). Neoplasm does not seem to require further consideration. In 1902 Spiller[2] described a case of unilateral hydrocephalus due to a small nodule obstructing the foramen of Monro. From the description he gives in the text, this did not seem to be neoplastic. In 1932 Tinel and co-workers[3] reported the gross findings in a case of unilateral hydrocephalus in which the ependyma

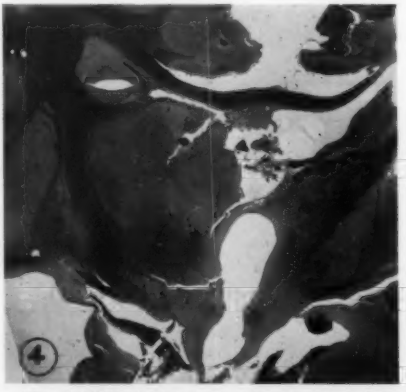
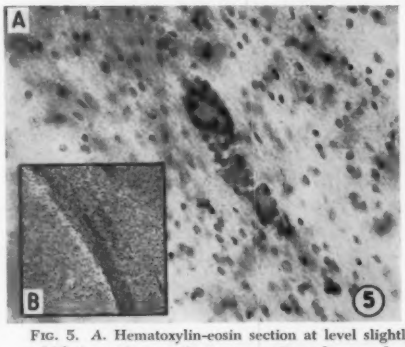


FIG. 4. Weigert-stained coronal section at caudal limit of left foramen of Monro. The choroid plexus is visible in the left lateral and third ventricles but not in the right lateral. A large amount of thalamic tissue is present on the right, occupying the site usually occupied by the lateral ventricle.



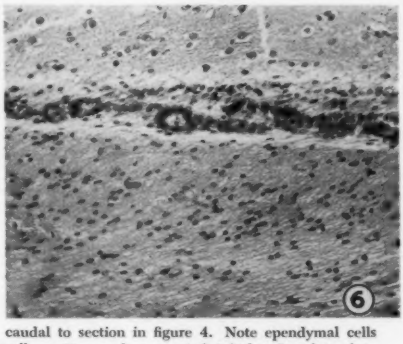


FIG. 5. *A*. Hematoxylin-eosin section at level slightly caudal to section in figure 4. Note ependymal cells which in various sections were patterned as cords, small rosettes, and segmented tubules dorsolateral to the right thalamus, where parts II and III of the lateral ventricle ordinarily would be found. Insert *B* shows low power section from which A was taken.

FIG. 6. Hematoxylin-eosin section at level which should ordinarily correspond to the frontal horn of the right lateral ventricle. Ependymal cells are seen arranged as cords, small rosettes, and tubules.

appeared gray and thickened and a membrane occluded the foramen of Monro, and in 1927 Dott[4] reported a similar instance considered to be of inflammatory origin. Patten[5] reported overgrowth of the walls of the embryonic cerebral vesicles, which resulted in a marked infolding and abnormality of the cerebral convolutions, but described no instance of obliteration of the lateral ventricle. None of the above conditions was encountered in the present case.

It is the opinion of the authors that the pathologic process in this case is similar to that which occurs in atresia or "forking" of the aqueduct. Russell[6] pointed out that the condition should be distinguished from stenosis of the aqueduct. In the former, the aqueduct is represented by two or more distinct channels, the usual single canal having been "broken up"; in the latter, the usual single canal is present but its lumen is abnormally small.

Many of the cases of aqueductal stenosis reported in the literature have been considered of inflammatory and/or gliotic origin.[7–10] Dandy's[7] opinion that unspecified toxins were responsible for these pathologic changes was seemingly shared by other authors. Parker and Kernohan[9] alluded to cases in the literature which showed no gliosis. They asserted, ". . . it is probable that the majority of cases of subependymal proliferation, with occlusion of the aqueduct of Sylvius, have an inflammatory or toxic basis, and that a few in which the hyperplastic changes are confined to the region surrounding the aqueduct owe their origin to a developmental error analogous to the changes normally occurring around the central canal of the spinal cord." Russell[6] reported two cases of aqueductal stenosis of the "congenital" type, in one of which there was an associated maldevelopment of the corpora quadrigemina. She felt that such cases are rare as compared to those of inflammatory or gliotic origin. Referring to Gerlach's work on variation in size of the aqueduct at various levels, she cautioned against mistaking a normal variation as an abnormal narrowing of the aqueduct.

We prefer the term "forking," suggest-

ed by Russell, for the condition commonly referred to as "atresia" of the aqueduct of Sylvius, since microscopic examination reveals a subdivision into multiple channels rather than the absence of the iter. There is general agreement in the literature that this condition represents a congenital anomaly. Russell[6] called attention to the frequent association of forking with malformations of the midbrain and other more remote organismic anomalies. Similarly, Roback and Gerstle[11] noted the association of spina bifida, club foot, and deformities of the toes.

Spiller[12] postulated that the closing in of tissue forming the aqueduct in the embryonal period might be carried beyond the normal degree and terminate in an almost complete stenosis. Kernohan[13] held a similar view. However, Roback and Gerstle[11] contended that the anomaly results from a failure of cells to migrate out from the central germinal layer in the usual fashion. They considered the process one of derangement and proliferation of cells in the ependymal layer, thus compromising the central canal.

Irrespective of the mode of maldevelopment it seems likely that some disturbance of the normal developmental pattern occurs. The region of the aqueduct is a relatively large caliber tube in the early stages of the embryo and, in the normal course of development, as Patten[14] points out, "with the great thickening of its walls the lumen of the mesencephalon becomes relatively reduced to form a narrow canal. . . . " The cerebral hemispheres begin as out-pocketings, the cerebral vesicles, from the telencephalon of the neural tube. The openings which connect the cavity of these vesicles with that of the telencephalon become in later stages of growth the foramina of Monro. At this early stage their caliber is relatively large in relation to the cavities of the telencephalon as compared to its relatively small caliber in the later stages of hemispheral development. The thin roof plate of the forebrain is carried out into the cerebral vesicles, and through it the choroid plexus invaginates into the cavities of the vesicles. In the final stages of development the choroid plexi of the lateral ventricles appear to connect with that of the third ventricle via the foramina of Monro. In the case here presented the right cerebral hemisphere was present and exhibited the posterior and inferior parts of the lateral ventricle and a choroid plexus. The evidence suggests that at some period in embryonic development an "overgrowth" of cells occurred, obliterating the anterior portion of the lateral ventricle and the foramen of Munro. As revealed in figures 5 and 6, the ependyma-lined cavity of the lateral ventricle has been "broken up" into multiple channels similar to that seen in forking of the aqueduct.

The pathogenetic factors held responsible by various authors for embryonal anomalies are numerous.[15,16] The increased incidence of anomalies associated with diseases of the mother, especially the exanthemata occurring in the first trimester, is also well documented. Experimental work by Spemann[17] has demonstrated the presence of chemical "organizer substances" within the embryo which influence its development. The teratogenous influence of external stimuli, such as heat and x-radiation, has been recently demonstrated by Gilchrist[18] and Hicks,[19] respectively. Campbell[20] pointed out the influence of the surrounding mesenchyme on the devel-

opment of the neural axis and emphasized the importance of temporal factors as determinants of the destiny of neural structures.

The factors influencing the development of the embryo are multiple, and the sharp distinction between heredity and environment, which until recently characterized conceptual thinking and writing in the biologic area, no longer appears warranted. The complex subtle changes which occur in the environment of the embryo and influence development and maturation are just beginning to be explored. The present case, in which a normal ventricle developed on one side and a "forking" on the other, suggests that the anomaly resulted from a process acquired *in utero*, rather than from a genic determinant. To our knowledge, the case is unique. Its significance appears to reside in its potential, if and when combined with data derived from similar cases that may in the future be reported, for ascertaining the time period within which such anomalies of the embryonic brain must be initiated.

SUMMARY

1. A case of unilateral obliteration of the anterior portion of the right lateral ventricle and the foramen of Monro attended by hydrocephaly is reported.

2. A comparison is made between the maldevelopment in this case and that of "forking" of the aqueduct of Sylvius. Certain factors which may contribute to such abnormalities are discussed.

3. A comparison of the anatomic findings of this case with familiar embryologic sequences suggests that the cerebral vesicle probably developed normally up to a certain stage and that some local factor or factors then supervened to produce obliteration of the foramen of Monro and part of the lateral ventricle.

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Methods of Evaluation of New Anticonvulsant Compounds

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IN RECENT YEARS a spate of new compounds has been introduced for the treatment of seizures, but the conflicting reports of their clinical efficacy and toxicity have caused confusion in the evaluation of these antiepileptic drugs and the general acceptance of some urgently needed and more effective agents in the treatment of epilepsy has inevitably been delayed. The rapid advances made in the development of new pharmacologic agents have contributed much to modern progress in the management of seizures, but without a careful appraisal of their clinical usefulness the continued laboratory investigation of such compounds will be hindered. The clinical evaluation of new anticonvulsants is, therefore, reviewed and, so that more consistent and significant results may be obtained, methods for the introduction of controls in antiepileptic drug trials are discussed.

Though the final evaluation of new anticonvulsant compounds must depend upon careful clinical trial, the testing of large numbers of potentially effective chemicals on human patients would be both hazardous and impractical and, for the preliminary studies on new drugs, laboratory assay technics are essential.

LABORATORY METHODS

Diphenylhydantoin (Dilantin), which marked a signal advance in the medical therapy of seizures, was the first anticonvulsant to be introduced as a result of extensive initial trials in animals with experimentally induced convulsions.[1] A battery of tests has since been designed to measure the potency of drugs potentially useful in convulsive disorders. The experimental seizures employed are of four main types: 1) electroshock, 2) chemical, 3) audiogenic, and 4) those induced by chronic epileptogenic lesions. Of these, the electrical and chemical methods of assay are used routinely, and since no single test yet available is entirely adequate, at least four procedures are applied. In one method the ability of the drug to protect animals from pentylenetetrazol (Metrazol) induced seizures is estimated. Electroshock seizures are produced by 60-cycle alternating current applied for 0.2 second through corneal electrodes, and the effectiveness of the drug is measured by

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its ability to raise the threshold for minimal (clonic) seizures or to modify the pattern of maximal (tonic-clonic) seizures. These technics have been described in detail by Swinyard[2] and other investigators. A new assay procedure developed by Toman[3] is based on seizures which resemble the clinical psychomotor type and which are evoked by low frequency stimulation.

Since all compounds of established value in the treatment of clinical epilepsy exhibit anticonvulsant activity by one or more of these laboratory tests, the value of such preliminary methods for screening potentially useful drugs is patent. However, in the prediction of potency, toxicity, and specificity of action in the various clinical types of seizures, the laboratory procedures have some limitations and the ultimate usefulness of an antiepileptic drug can be determined only by actual clinical experience.

CLINICAL METHODS

The new anticonvulsant should be examined clinically with regard to potency, toxicity, rapidity and duration of action, and specificity for the various types of seizure patterns. Goodman and Gilman[4] have defined the properties of an ideal antiepileptic drug. It should be nonsedative, well tolerated, highly effective against various seizure types, and devoid of untoward effects on vital organs and functions. In addition, it should exhibit rapidity of action on acute parenteral injection in the control of status epilepticus, and its effect must be of long duration following oral administration in the treatment of recurrent seizures. A preliminary estimation of potency may be obtained by observing the effects of the drug on therapeutic electroshock convulsions in psychiatric patients and on seizure discharges in the electroencephalogram.

The relative effects of conventional anticonvulsant agents on the electroshock seizure pattern were investigated by Toman, Loewe, and Goodman[5] in patients who received convulsive therapy for psychiatric disorders. Dilantin, in nontoxic doses, and methylphenylethyl-hydantoin (Mesantoin) consistently abolished the tonic phase of the seizures, and phenobarbital, sodium bromide, and mephobarbital (Mebaral) were effective but only in doses which occasionally produced undesirable side effects. Trimethadione (Tridione), when given in doses more than adequate to control clinical petit mal seizures, was ineffective and did not modify the electroshock seizure pattern. Prior to the electroshock treatment, the drugs were administered in divided doses for a length of time sufficient to ensure the maximal effect and, in order to obtain a true measure of the potency of a new anticonvulsant by this method, an initial determination of the optimum dosage and the time of peak effect is essential.

Therapeutic electroshock in psychiatric patients has since been employed for the preliminary clinical evaluation of new compounds, which on previous laboratory testing had exhibited anticonvulsant activity; SKF No. 2599 (5,5-diphenyl-tetrahydroglyoxaline-4-one), when compared with Dilantin, was found to possess definite advantages and, in a subsequent prolonged clinical trial in epileptic patients, the superiority of the new chemical was also apparent.[6,7]

The ability of the new compound to suppress seizure discharges in the electroencephalogram may be of some value in the prediction of its clinical effective-

ness. Seizure discharges, which formerly could be induced by hyperventilation, Metrazol, or other activating procedures, may be prevented by the drug following its acute administration. Tridione, of specific value in the treatment of true petit mal, will abolish the spike-and-wave discharge associated with these seizures. It must be emphasized, however, that a negative response does not necessarily detract from the potential therapeutic value of a drug; acetazoleamide (Diamox), on intravenous injection in two patients, had no immediate effect on the three-per-second, spike-and-wave electroencephalographic discharge,[8] while it is said to be effective in the treatment of petit mal seizures.[9]

The relative potency of several new compounds may be assessed rapidly and with a reasonable degree of safety by these preliminary methods, but the measure of usefulness of an anticonvulsant drug is not its absolute potency but its therapeutic index, or the ratio of the toxic and effective doses. This margin of safety of a compound and its practical value in the treatment of recurrent seizures may be determined only by prolonged and controlled trial in epileptic patients.

DIAGNOSIS AND CLASSIFICATION OF SEIZURES

An accurate diagnosis must be established before treatment is begun, and the seizures should be classified as to etiology, the anatomic localization, and the clinical and electroencephalographic pattern. It is essential to exclude from the trial patients with metabolic disorders in whom seizures are the result of glucose, calcium, parathyroid, or pyridoxine deficiency, and those whose seizures are readily amenable to surgery or other specific therapy. The seizures of organic etiology which are associated with a demonstrable brain lesion must be distinguished from the cryptogenic type. The former are sometimes refractory to therapy, while the latter are usually responsive.

The specificity of action of some currently employed anticonvulsants is related to the clinical pattern of the seizure and sometimes to the electroencephalographic abnormality. Major seizures, both generalized or grand mal and those with focal manifestations, are responsive to phenobarbital, Dilantin, and primidone (Mysoline). In the control of psychomotor or temporal lobe seizures, phenylacetylurea (Phenurone) is remarkably effective, though the use of this drug is limited by its toxicity.

Minor seizures of three types, true petit mal, akinetic, and myoclonic, have been described and the electroencephalogram is of particular value in their differentiation. The true petit mal or "petite absence" is associated with a bilateral three-per-second, spike-and-wave discharge, while the two-per-second, slow spike-and-wave is the electroencephalographic pattern most commonly seen in children with akinetic seizures.[10] The third type of minor seizure, the myoclonic jerk, is accompanied usually by a multiple spike-and-slow wave discharge. Abortive major or "minor motor" seizures may resemble petit mal clinically, but the electroencephalographic complex characteristic of true petit mal is rarely seen.

According to the anatomic classification of seizures, it is suggested that all forms of the "petit mal triad" have a common subcortical or centrencephalic origin. From a therapeutic standpoint, however, it is important to distinguish

true petit mal from akinetic and myoclonic seizures. While the former respond to the oxazolidinediones (Tridione and Paradione) and to the succinimide compound, Milontin, the latter are controlled more successfully by drugs effective in major epilepsy. In a trial of Milontin, children with true petit mal were well controlled, while those with akinetic attacks were benefited rarely. In addition to this variation in response to therapy, the clinical features of these patients differed widely. In the group of children with akinetic seizures, the high incidence of major convulsions, brain damage, and mental retardation was remarkable, while in the group with true petit mal these complications were only rarely apparent.[8] Lennox and Davis[10] have reported a high incidence of brain damage and subnormal mentality in children with seizures associated with the slow spike-and-wave discharge in the electroencephalogram, while in patients with the fast spike-and-wave discharge the incidence of neuropathologic changes was minimal. In the former group of patients the response of the seizures to Tridione was poor, but in the latter group a high percentage was controlled.

The response to drug therapy may, therefore, be related to the clinical and electroencephalographic patterns, the etiology of the seizures and, in the evaluation of new anticonvulsant compounds, the specificity of action should be determined accurately by controlled clinical trial.

USE OF CONTROLS

The diversity of reports on the efficacy of new antiepileptic drugs points to the necessity for controlled studies and evaluations based on scientific experimental design. The influence of psychologic factors on the incidence of seizures is well known, and an initial beneficial effect may be expected with any new form of therapy.

In the treatment of recurrent seizures the anticonvulsant action must be sustained, and a period of at least three months is necessary in order to assess the practical value of the new drug. During this prolonged trial numerous factors may alter the threshold to seizures, and the evaluation of the drug under investigation may thus be invalidated. Exacerbation of seizures may result from hydration, fever, and fatigue, while remission may follow an environmental change or may occur spontaneously. It is difficult, therefore, to be certain that a reduction of seizures observed during chronic administration of a new drug is a result of the therapy and, without the use of controls, the conclusion that the *post hoc* means *propter hoc* cannot be convincing.

The Metrazol seizure threshold has been used to test anticonvulsant drug action in epileptic patients but, until a more practical and reliable method of measurement of the seizure threshold is found, the response to therapy may be assessed only by careful observation of the patient for the occurrence of seizures. The greater the incidence of seizures prior to commencement of the medication, the more suitable is the patient for inclusion in the trial. An accurate record of the occurrence of major seizures is possible in a hospital environment, and ideally the initial clinical trial of a new drug in patients with grand mal should be performed in an institution where medical and nursing attention is readily available should untoward effects or status epilepticus develop. A

more exact record of minor seizures may be obtained in the home environment and in school but, before selection of the child, a reasonably constant degree of surveillance by the parent and school teacher must be assured and the reliability of these observers must be assessed. A printed form is provided on which to record the number of seizures each day and any unusual symptoms or signs which may occur. The patient is seen at frequent intervals for clinical examination and for blood, urine, and liver function tests.

In some drug trials, accepted opinions of the patient or a parent regarding the incidence of seizures prior to medication have been compared with the incidence observed during the trial. Unfortunately, these opinions are not infallible and, unless the effects of the new treatment are dramatic and the seizures are completely controlled, an evaluation based on such evidence is not convincing.

In pharmacologic trials the design of the experiment may involve control periods or simultaneous controls.[11] Each individual patient may be used as his own control by keeping him under observation for a period of time before the new treatment is applied; but, owing to the many factors which are known to influence the seizure threshold, the control period must be long and the effect of treatment immediate if the assessment of results is to be reliable.

Evidence based on simultaneous controls is more satisfactory, and the use of paired controls provides the most efficient experimental design and one which will give significant results with fewer observations. The patients must be hospitalized in the same environment, and each patient treated with the new drug is paired with a control who should be similar as regards age, sex, and seizure incidence. Since epilepsy is not a disease in itself but a symptom complex which varies widely in etiology and clinical manifestations, the control of all possible variables is unlikely. To offset this difficulty of paired selection, a larger number of patients is necessary to obtain significant results. The patients are allocated to the trial or control group at random so that, apart from the treatment under study, there is no systematic difference in the factors which may influence the incidence of seizures in the two groups.

If the trial is in clinic patients, alternate allocation of cases to the two groups may be used but, in order to avoid bias in both the allocation and the assessment of results, the double blind technic must be employed. The control medication and the drug under trial must be indistinguishable in appearance, taste, and odor and, until the evaluation is completed, neither the patient nor the doctor should have knowledge of the code. In one such experiment[12] in patients with minor seizures who were selected only according to age group and seizure type, four preparations were employed, of which two were the drug under trial and two were a dummy control. They were prescribed in serial order to successive patients who attended the clinic, and the alternate preparation was substituted after six weeks and was given for an equal period.

In patients with major seizures, the use of dummy controls is precluded by the danger of status epilepticus which may occur on withdrawal of the active drug. However, a new compound to be accepted for general use must prove superior in efficacy or less toxic than the anticonvulsants of established value.

Provided that evidence of an anticonvulsant effect has previously been obtained by laboratory and preliminary clinical tests, the action of the trial drug may be compared with that of the currently accepted treatment of choice. By the use of active medications as controls, the clinical trial based on scientific method is ethical and without hazard in patients with major seizures, and a significant evaluation of the new drug is made possible. In institutionalized patients for whom constant medical supervision is available, existing medication may be withdrawn cautiously at the commencement of the trial, but in clinic patients this procedure is practical only in those with minor seizures.

DOSE RESPONSE

In a comparison of the effects of two drugs, the relation of the dose to the observed response must be considered and, since the individual response varies widely, a single arbitrarily pre-determined dose for all patients cannot be employed. Sedation and other untoward effects of some anticonvulsants are less likely to occur if the initial dose is small and increments are made slowly. The dose should be increased until complete control of seizures is obtained or toxic effects ensue, and the comparison of the new and the control medication should be based upon the incidence of seizures during periods of treatment with the maximally effective or largest tolerated doses.

INCIDENCE OF TOXICITY

Since the efficacy of many antiepileptic compounds is limited by their toxicity, an assessment of the margin of safety of the trial drug is important in its evaluation. If the incidence of serious side effects such as leukopenia, liver injury, and nephrosis is high, the use of such a compound must be restricted to the treatment of seizures refractory to less noxious agents. Untoward reactions which involve the central nervous system (ataxia, sedation) and gastrointestinal tract (nausea, vomiting) are usually benign and of no danger to the patient's life; they limit the usefulness of a drug only when the effective dose approximates the toxic dose.

In the recommendation of a new anticonvulsant for general use, the conservatism which stems from caution must be tempered by the urgent need for new and improved agents in the treatment of epilepsy. In some cases the use of drugs which involve a certain risk may be warranted, but the hazard of the remedy must be compared with the severity of the symptom and, in patients with infrequent seizures of the petit mal type, the use of a potentially toxic therapeutic agent cannot be condoned.

When a true assessment of the value of a new anticonvulsant has been obtained by the methods described, the response to the drug may be correlated with the etiology, anatomic localization, and clinical and electroencephalographic pattern of the seizures. A reliable therapeutic classification of seizures could then be developed, from which fundamental information might be derived concerning the specificity and mechanism of action of anticonvulsants and the nature of the seizure process.

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■ How is it that there is not an evident decussation of many, if not all, the fibres of the posterior roots in the spinal cord? Vivisections, and, as we shall show, pathological cases establishing positively the necessity of admitting the existence of such a decussation, it seems certainly strange that we do not see a manifest and considerable decussation between the continuations of the fibres of the posterior roots in the spinal cord. It may be that some of the fibres which cross each other in front of the central canal of the cord are not, as now admitted, fibres of the anterior roots, but fibres of the posterior ones, which, after having passed obliquely from the posterior parts of the cord into the anterior, become transversal there, and pass horizontally into the other lateral half of the cord. But, whatever may be true in this respect, there are conductors connected by means of cells with the fibres of the posterior roots, and they pass from one lateral half of the cord into the other one. They have been seen and described, and represented more or less clearly, by most of the micrographers who have recently published papers and plates on the organization of the spinal cord. We will name only R. Wagner, Lenhossek, Schroeder Van der Kolk, Bidder and his pupils (Kupfer, Owsjannikow, Metzler) Stilling and Gratiolet. According to the actual teachings of microscopical examinations of the spinal cord, many of the fibres of the posterior roots reach the cells of the gray matter on their own side, and these cells send fibrils to cells which are in the other half of the spinal cord, and these last cells send fibrils upwards towards the encephalon. This organization is assuredly sufficient to explain the crossed transmission of sensitive impressions.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Carotid Artery Occlusion

J. E. Webster, M.D., E. S. Gurdjian, M.D. and F. A. Martin, M.D.

THE FREQUENT OCCURRENCE of thrombosis involving the carotid arteries in the neck has gained recognition during the past five years. Neurosurgeons have discovered this frequency as a result of angiographic studies of patients having symptoms and signs of cerebrovascular disease. Pathologists are confirming the clinical findings in autopsy studies. Clinicians are recognizing that this disease has many neurologic manifestations ranging from vague sensory symptoms to profound paralysis.

This material is a summary of findings in 70 patients with carotid artery occlusion referred to a neurosurgical service for diagnosis. During this period approximately 803 angiograms were performed. Since only a limited number of the patients admitted to the hospital with "stroke" syndromes were studied by angiography, this incidence of the lesion is impressive.

Carotid artery occlusion, when complete, can be identified by an obvious roentgen pattern as the contrast medium is arrested in its upward flow into the brain (figure 1). Radiographic evidence of partial occlusions is less obvious but is apparent in some of the angiographic studies which we have made (figures 7 and 8). The partial occlusions are usually located at the beginning of the internal carotid as it leaves the carotid bulb. The effect of such occlusions upon blood flow would seem to be significant since such dynamics are related to the diameter of the vessel and thus the degree of occlusion.

What has been identified in the past as the "carotid sinus reflex," involving loss of consciousness upon compression of the carotid bulb, has been observed

FIG. 1. *J. P.* (age 48). Complete obstruction of the left internal carotid. This is the most frequently encountered angiographic pattern. Aphasia was the only focal sign present.

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This work aided by a grant from the Kresge Foundation.

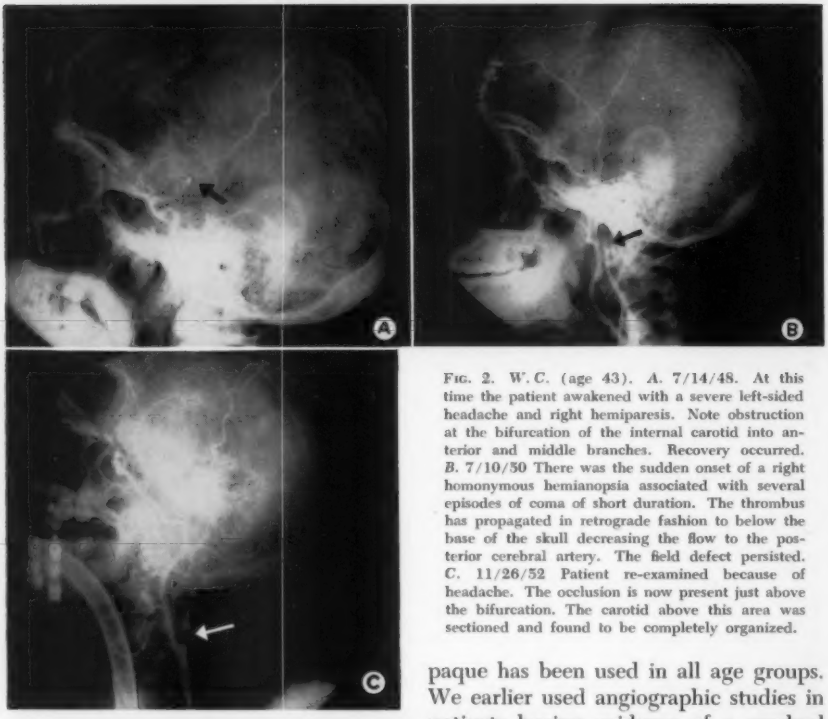


FIG. 2. W. C. (age 43). *A.* 7/14/48. At this time the patient awakened with a severe left-sided headache and right hemiparesis. Note obstruction at the bifurcation of the internal carotid into anterior and middle branches. Recovery occurred. *B.* 7/10/50 There was the sudden onset of a right homonymous hemianopsia associated with several episodes of coma of short duration. The thrombus has propagated in retrograde fashion to below the base of the skull decreasing the flow to the posterior cerebral artery. The field defect persisted. *C.* 11/26/52 Patient re-examined because of headache. The occlusion is now present just above the bifurcation. The carotid above this area was sectioned and found to be completely organized.

as a phenomenon present in patients with either a complete or partial carotid occlusion. Brief compression of the unoccluded carotid in some of these patients results in syncope without a change in cardiac rhythm, rate, or blood pressure. The electroencephalographic pattern suggests that cerebral ischemia occurs under these circumstances (figure 9).

METHOD

The angiographic studies in this group of patients were as a rule made by the closed method of injection, using Thorotrast as the contrast medium in all patients above the age of 50 or in those sensitive to Diodrast. More recently, Hypaque has been used in all age groups. We earlier used angiographic studies in patients having evidence of a cerebral hemorrhage. The indications have now been broadened to include all patients with major "stroke" syndromes and in those having recurrent "strokes" with or without bloody spinal fluid.

The contrast roentgenograms are made to visualize not only the cerebral circulation but also to delineate the outline of the carotid bulb in the neck. The injection of the contrast medium is therefore made into the common carotid artery. Many of the studies are made

TABLE 1

INCIDENCE IN AGE GROUPS

Decade of Life	*2nd*	*3rd*	*4th*	*5th*	*6th*	*7th*
Number of cases	1	10	10	27	15	7

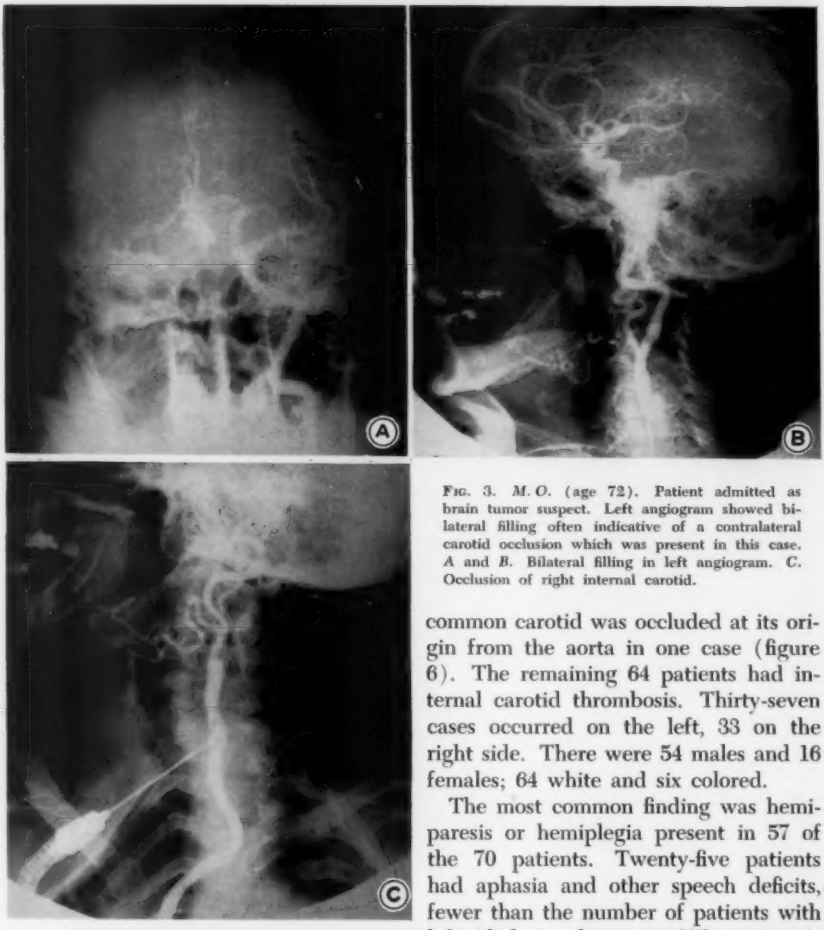


FIG. 3. *M. O.* (age 72). Patient admitted as brain tumor suspect. Left angiogram showed bilateral filling often indicative of a contralateral carotid occlusion which was present in this case. *A* and *B*. Bilateral filling in left angiogram. *C*. Occlusion of right internal carotid.

under local anesthesia. Complications of this diagnostic procedure have been minor ones.

RESULTS

During the past five years 70 patients with thrombosis of the internal carotid artery or the carotid bifurcation have been encountered. The bifurcation was involved in five instances and the left common carotid was occluded at its origin from the aorta in one case (figure 6). The remaining 64 patients had internal carotid thrombosis. Thirty-seven cases occurred on the left, 33 on the right side. There were 54 males and 16 females; 64 white and six colored.

The most common finding was hemiparesis or hemiplegia present in 57 of the 70 patients. Twenty-five patients had aphasia and other speech deficits, fewer than the number of patients with left-sided involvement (37 patients). Headache was a complaint in 15 cases. Thirteen patients had abnormal mentation. Twelve cases had hemihypalgesia or hemiparesthesias. Ten patients entered the hospital comatose. Nine cases had a monoplegia, eight a monohypesthesia. Six patients had seizures; two had jacksonian and four had generalized seizures. Four patients presented an op-

TABLE 2

Symptom or Sign	Incidence of Symptom or Sign	Onset		Number of Episodes		Time of Onset	
		Abrupt	Insidious	Single	Multiple	At rest	During activity
Hemiplegia or hemiparesis	57	50	7	38	19	11	46
Aphasia	25	23	2	16	9	2	23
Cephalgia	15	13	2	8	7	5	10
Abnormal mentation	13	8	5	7	6	8	5
Hemianesthesia or hemihypalgesia	12	9	3	4	8	4	8
Coma	10	9	1	9	1	2	8
Monoplegia or monoparesis	9	9	0	6	3	4	5
Visual disturbances	8	7	1	4	4	3	5
Paresthesias of one extremity	8	8	0	5	3	2	6
Seizures	6	6	0	0	6	5	1
Homonomous field defect	3	3	0	2	1	0	3
Optic atrophy	4	3	1	1	0	0	4

tic atrophy. Three had a homonymous field defect. In two cases the cerebrospinal fluid was bloody. In 50 of 57 patients the hemiplegia had an abrupt onset. Thirty-eight of 57 had the hemiplegia or hemiparesis as the first manifestation of the illness. Among those with hemiplegia or hemiparesis, the disability developed while the patients were active in 46 cases. The onset of other disabilities was similarly abrupt. Fifty-six of 70 had normal blood pressure levels. Three in the group had diabetes and eight had vascular disease elsewhere in the body. Five of the entire group died in the hospital at the time of the first admission. Four others died in the hospital upon readmission.

A total of 38 patients were examined by electroencephalography. There were repeated examinations in six. Thirty-two electroencephalograms showed focal abnormality, three had generalized abnormality, and three were normal. Fourteen patients had a delta and focal dysrhythmia. Thirteen patients had delta alone and four patients had focal dysrhythmia alone.

Unconsciousness from compression of the contralateral carotid was studied by electroencephalography in some of these patients. The record was done during digital pressure on the carotid artery. In one instance (figure 9), the patient experienced a "funny" feeling followed by loss of consciousness. Unconsciousness occurred after seven, 16, and ten seconds of pressure and lasted six, ten, and five seconds, respectively. In each instance generalized rhythmic slowing most marked anteriorly and temporally occurred. This occurred about one or two seconds before interruption of consciousness and corresponded approximately with the "funny" feeling.

Among patients with repeated routine studies, four showed improvement in the electroencephalogram and one remained essentially the same. The patient whose electroencephalogram did not improve also showed a disability which remained unaltered. The patients with normal electroenecphalographic records were chronic hemiplegics.

The angiographic findings showed the presence of an internal carotid artery

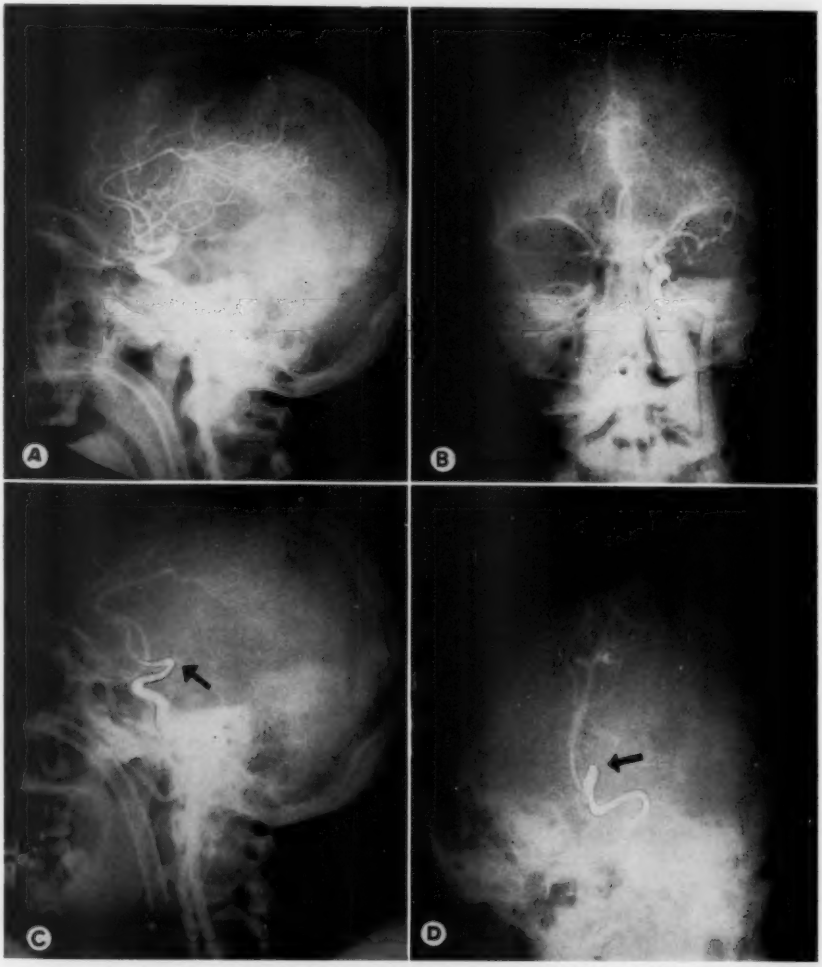


FIG. 4. G. S. (age 34). 3/14/50 Numbness of the right arm, face, and tongue in episodes. Then a sudden episode of aphasia and right hemiparesis. A similar episode had occurred six years before from which there was complete recovery. *A* and *B* show a normal angiogram. On 3/19/52 there was an episode of numbness of the right hand and arm associated with occipital headache and aphasia. Right hemihypalgesia and aphasia noted. *C* and *D* reveal that a thrombosis of the middle cerebral had occurred. Pneumoencephalogram was normal.

thrombosis in 58 instances, a thrombosis at the level of the siphon in five cases, thrombosis at the middle cerebral artery in four patients, at the anterior cerebral in two, and at the posterior cerebral in one.

FIG. 5. *F. C.* (age 53). Occlusion of the right internal carotid at the base of the skull associated with a left hemiplegia and aphasia and subsequent improvement.

PATHOLOGIC FINDINGS

In this series, 41 patients had an exploration of the neck and excision of a portion of the thrombosed vessel near the bifurcation. The external carotid artery was spared because it was felt that the external carotid artery may be of value for collateral circulation to the intracranial contents through its frontal and supraorbital branches. In four cases the entire bifurcation was excised.

The thrombosed internal carotid artery was either swollen and sausage-like or atrophic and collapsed. In only one instance was there bleeding from the distal portion of the vessel suggesting that the vessel might have been patent above the level of the thrombosis. In three patients elongated and relatively fresh clots were removed from the distal portion of the vessel, but this was not followed by bleeding (figures 10, 11, and 12).

Palpation of the bifurcation in patients with thrombosis of the internal carotid revealed a calcareous mass involving the carotid bulb. At times the

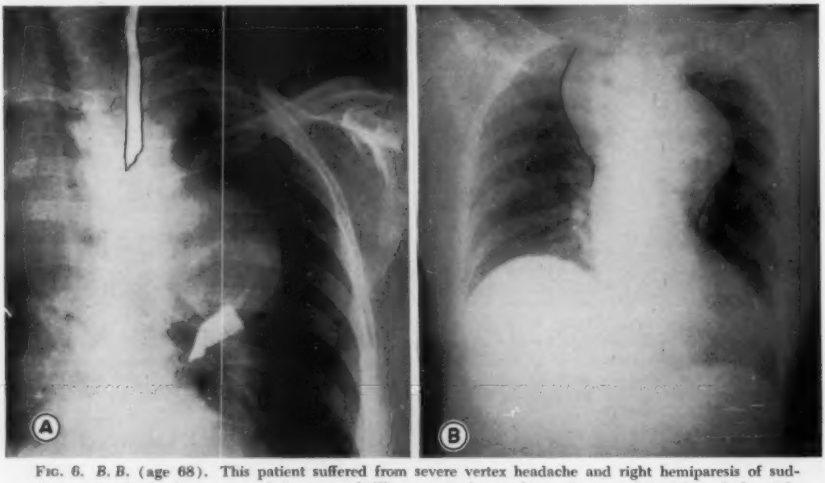


FIG. 6. *B. B.* (age 68). This patient suffered from severe vertex headache and right hemiparesis of sudden onset. *A.* Angiogram revealed a normal filling cerebral vasculature but an obstruction of the right common carotid at its origin by an aortic mass. No pulse could be detected. Open angiography was necessary. *B.* Routine chest plate which reveals the thoracic mass producing occlusion of the common carotid.

FIG. 7. *A. C.* (age 60). Incomplete occlusion of the left internal carotid. There were two episodes of right hemiplegia and aphasia seven years apart. Compression of the ipsilateral or contralateral carotid sinus in this type of patient may result in unconsciousness and/or hemiparalysis without cardiac inhibition. FIG. 8. *J. D.* (age 63). An example of incomplete right internal carotid occlusion. The patient had recurrent attacks of left hemiparesis culminating in paralysis. Compression of the right carotid sinus resulted in syncope with normal blood pressure and electrocardiogram. The electrocardiogram and electroencephalogram are also shown in figure 9.

calcareous matter was so extensive that it seemed unusual that the external carotid artery was still patent. In many instances the external carotid artery appeared to be quite large compared with the internal, appearing to have undergone compensatory dilatation.

The microscopic findings varied depending upon the level of section of the carotid and also the time after the onset of the disease. All cases showed evidences of atherosclerosis. When the microscopic material came from the artery near the bifurcation, fibrosis, cholesterol deposits, and endothelial ulcerations with fibrin clots clinging to the area of the damage were seen. In those instances where complete organization had taken place, vessels were noted in the organized artery suggesting an attempt at canalization. We have not seen an example of canalization which appeared to be functioning. In early cases, the lumen was occluded by a fresh clot but atheromatous changes in the vessel wall were prominent.

Autopsy studies are now supplying important information on this aspect of the disease. Fisher[1] has analyzed findings from 432 consecutive autopsies in which the brain and carotid arteries were studied. Of these 432 "routine cases," 28 (6.5 per cent) had complete occlusion of one or both carotid arteries. Thirteen showed "very severe narrowing" of the arterial lumen making a total of 9.5 per cent having "advanced carotid disease." Most of the cases presented the thrombus within the carotid distal to the blocked sinus. In four cases it was found that the primary occlusion was intracranial and retrograde thrombosis had occurred back to the region of the carotid sinus. Hultquist[2] noted

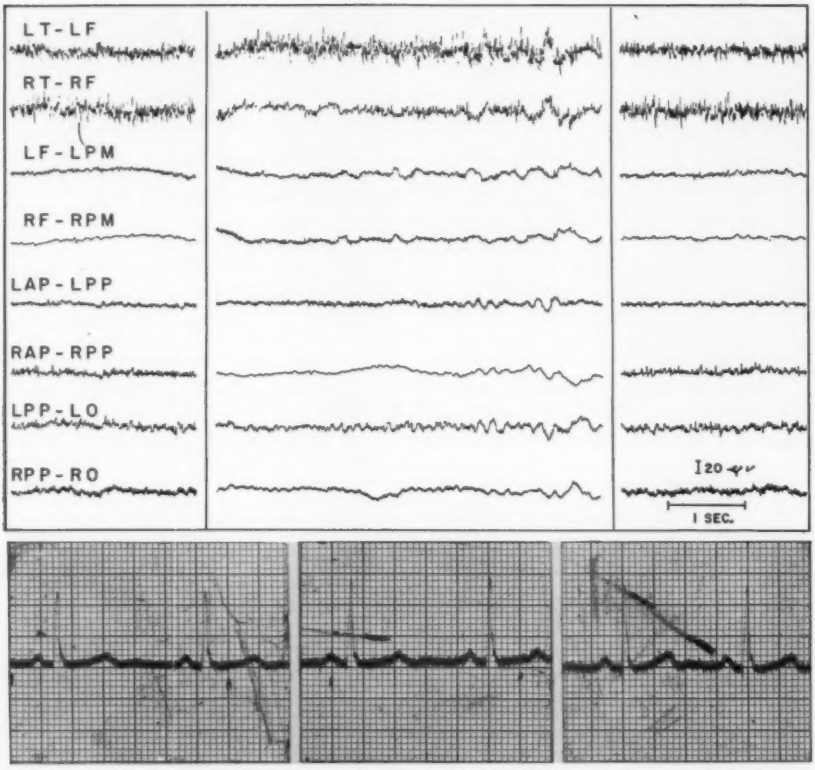


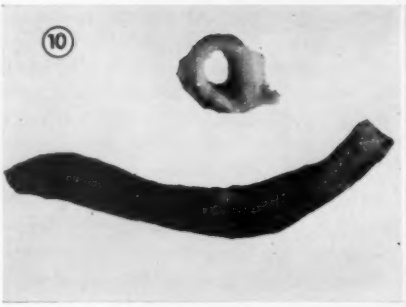
FIG. 9. *J. D.* (age 63). Patient presented incomplete occlusion of right carotid (figure 8). Compression of the contralateral carotid (left) resulted in syncope with flattening in the electroencephalographic record. No change occurred in the electrocardiogram (below).

that the primary site of occlusion had occurred near the origin of the ophthalmic artery in one-third of his cases.

Fisher[1] pointed out that pathologic findings indicate that the atherosclerotic plaques within the carotid sinus are prone to ulcerate and a mural thrombus then forms at this point. Emboli arising from such mural thrombi were found in four cases. Fisher found ten cases of "bilateral carotid disease," apparently with thrombosis, in his studies. We have encountered three cases. Angiograms have been done without complication in patients with unilateral occlusions by injection of the contralateral patent artery. Bilateral filling usually occurs. When this type of angiographic pattern is encountered in a routine angiographic study it suggests the possibility of contralateral occlusion (figure 3).

COMPLETE OCCLUSION

Information concerning complete occlusions of the carotid arteries has appeared in the literature from time to



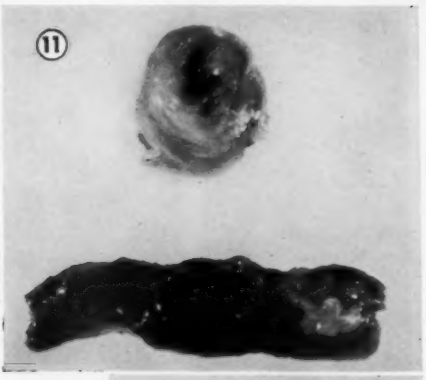


FIG. 10. *H. C.* (age 63). This internal carotid was occluded at the bifurcation. The above is a section made just above the bifurcation of the common carotid. A recent thrombus was pulled from the distal arm with ease. The length of the thrombus corresponds to the distance from the bifurcation to the base of the skull. No retrograde bleeding occurred.

FIG. 11. *A. L.* (age 71). Above is the totally occluded internal carotid artery. Below is the partially organized clot which was pulled free from the distal end of the internal carotid in the neck. No retrograde bleeding occurred.

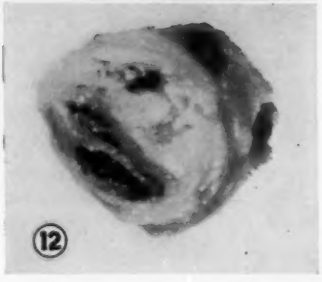


FIG. 12. *A. E.* The carotid bifurcation seen from its superior aspect. The larger lumen is the external carotid. Note the diffuse involvement of the entire bifurcation with fibrous proliferation. It is most marked about the internal carotid, which was occluded and contained a fresh clot.

time for many years. Observations were reported upon carotid thrombosis in relationship to ligation of these vessels, trauma, and local disease in the neck including aneurysms. There were infrequent reports concerning spontaneous thrombosis of the carotid. The existence of this lesion was overlooked by both pathologists and internists and was not included in teaching textbooks. Kussmaul[3] in 1872 and Penzoldt[4] in 1881 reported several cases, but reports were meager until 1950. Moniz and co-workers,[5] Erickson,[6] Andrell,[7] Wolfe,[8] Galdston and co-workers,[9] and Chao and co-workers[10] presented cases prior to 1950. Since then, reports have appeared in many journals and texts.[11,12]

The clinical aspects of the condition are gradually being understood as surveyed cases multiply. In our own experience, we reported three cases of thrombosis of the common, internal, and external carotid arteries in 1950[13] and were impressed by the occurrence of a unilateral optic atrophy which was present in two of the patients, previously noted by Hunt.[14] In one patient (aged 23) the onset was explosive with an accompanying hemiplegia. In another (aged 65) only transient paresthesias had occurred over many years.

In 1953 when the neurologic findings in 30 patients had been analyzed and reported,[15] it appeared that, although acute paralyzing syndromes occurred in some and only minor symptoms and signs in others, the majority presented a progressive course of recurring paresis or paralysis of the arm, leg, or both.

FIG. 13. *M. J.* (age 63). Patient presented an occlusion of the right internal and external carotids associated with a chronic left hemiplegia (one year). Then acute popliteal occlusion as shown, indicating generalized atheromatous disease.

It was noted that palpation of the carotids did not reveal the diagnosis when only the internal carotid was involved. There was no way of confirming the diagnosis clinically except by angiographic study.

The additional observations on a total of 70 cases have emphasized the more frequent occurrence of occlusion of only the internal carotid artery rather than the common, internal, and external as was early encountered.

Emphasis also has been given to the principle that a diagnosis of "stroke," "cerebral thromobsis," "cerebrovascular disease," and "embolism" may be related to ischemia of the brain due to occlusive disease of the carotid artery, usually at the carotid bulb in the neck, either complete or partial due to atheromatous degeneration. Generalized atheromatous disease may be present and occlusions may occur also in other vessels (figure 13).

INCOMPLETE OCCLUSIONS

The impressive roentgenograms of complete occlusion of the carotid artery have diverted attention from abnormalities which may exist at the carotid bulb in cases in which the cerebral vessels are filled with the contrast medium. At times in our experience, we have failed to include the carotid bulb in the routine angiographic studies unless there is lack of filling with contrast media in the cerebral vessels. Greater attention to the site of the bulb area has shown distortions which suggest the presence of plaques, stenosis, and narrowing of the vessel through a varying distance. Prior to the production of a complete thrombosis of the internal carotid artery, there may be incomplete occlusion with reduced blood flow. Such an occlusive effect may result in ischemia of the brain, with "cerebrovascular accidents" of varying intensity and duration.

Of interest has been the observation that digital compression of the carotid opposite to that occluded may result in syncope. Transient unconsciousness has occurred after about 10 seconds of compression without a cardiac effect. Wright[16] stated that "the nerve endings in the carotid sinus in man can be stimulated by applying external digital pressure. Such compression produces the expected reflex cardiac slowing, vasodilatation, and fall of blood pressure. Very marked slowing may be obtained in arteriosclerotic subjects, probably because the sensory endings are pressed against the hardened media and so re-

ceive vigorous stimulation." Askey[17] has reported on the untoward results of mechanical stimulation of the carotid sinus in a summation of the experiences of members of the California Heart Association. Ten instances were reported; in seven a contralateral hemiplegia resulted. He stated that "a direct unilateral cerebral effect from carotid sinus pressure, therefore, would appear to be more important in our patients than the production of cardio-inhibition or vasodepression; that the cerebral effect was due to ischemia brought about by reflex vasoconstriction."

It would also seem probable that the brain ischemia directly resulting from the reduction in blood flow by the induction of bilateral carotid occlusion, complete or nearly so, could also account for important physiologic effects in some cases unrelated to carotid nerve endings and a vagal reflex or to vasoconstriction. The function of the basilar artery must also be given consideration. If flow is insufficient in this vessel, the compression of either carotid may result in syncope. The experiments of Heymans and Bouckaert[18] upon bilateral carotid occlusion in the anesthetized dog would not seem applicable to the human.

The clinical features of incomplete carotid occlusion seem to be obscured in the complexity of symptoms described in the past as "small stroke" syndromes, "light stroke," spasm of cerebral vessels, and "recurrent paralysis." The dynamics of such insufficiency can be understood by considering the basic principles involved in the flow of fluids through tubes.

Atheromatous plaques at the bifurcation are commonly seen by angiography with the angiographic pattern above this level being quite normal. The presence of an atheromatous plaque causing a narrowing and incomplete occlusion of the bifurcation may result in cerebral ischemia.

If occlusive plaques with symptoms are the forerunners of forward embolism or carotid artery thrombosis, then the possibility of excision of the bifurcation and re-establishment of the blood flow by a graft or reconstruction of the bifurcation are considerations worthy of careful study. Three patients have been treated by reconstruction of the bifurcation after excision of the atheromatous segment; each re-thrombosed.

Among several of the patients who had repeated attacks of cerebrovascular insults, the excision of the totally occluded internal carotid artery appeared effective in eliminating further attacks. This suggests the possibility of preventing forward embolism from the upper end of the clot mass. Forward embolism may be caused by the pulsation of the vessel at the lower end of the thrombus as well as by the mechanical effect of elongation of the vessel at systole with a pull upon this structure and its semisolid content.

The occasional dramatic effect resulting from stellate block in the neck or infiltrating novocaine about the artery may be related to a local carotid artery response with relaxation of a thrombosing vessel undergoing local spasm.

Pathophysiologic studies of this problem correlated with clinical findings give promise in answering many of the questions which are now obscure. This calls for a willingness by clinicians to revise their older and ingrained concepts concerning "strokes" inherited from Charcot[19] and Duret.[20] Neurosurgeons have the responsibility of proving that angi-

ography is no longer an experimental technic but a safe and revealing diagnostic procedure. The internist, neurologist, and general practitioner who first treats the "stroke" patient may then, with the assistance of the neurosurgeon, make new progress in dealing with cerebrovascular disease.

SUMMARY

1. During the past five years 70 patients with carotid artery occlusions have been diagnosed by angiographic studies.

2. The clinical neurologic findings are variable and range from mild symptoms of vertigo and paresthesias to hemiplegia. The condition simulates strokes and brain tumors.

3. Partial occlusion of the internal carotid artery at the carotid bulb by atheromatous plaques may also result in neurologic deficits. Angiographic studies should visualize the carotid bulb region.

4. Digital compression of the carotid bulb in patients with occlusive disease, partial or complete, may result in syncope. The mechanism of the "carotid sinus reflex" of the "cerebral type" may be accounted for on this basis rather than by "vasoconstriction." The sufficiency of the basilar artery also is important.

5. Complete carotid occlusions have been treated by surgical excision of a segment of the vessel to prevent forward emboli.

6. Incomplete occlusions present the possibility of treatment by means of an arterial graft.

7. The collaboration of the general practitioner, internist, and neurosurgeon, with the aid of angiography, can make new progress in the diagnosis and treatment of cerebrovascular disease.

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Acute Hemorrhagic Encephalitis

*Kristian Kristiansen, M.D., Wilhelm Harkmark, M.D. and Maynard M. Cohen, M.D.**

In 1891 Strümpell[1] suggested the designation of acute hemorrhagic encephalitis to describe a condition characterized pathologically by necrosis, hemorrhage, and demyelination in the cerebral white matter. In subsequent reports elaborating the pathologic features of this disorder, the lesions were often noted to be asymmetric, with one hemisphere exhibiting more severe damage than the other. Although the pathologic changes have been adequately described in fatal cases, the pathogenesis and responsible etiologic agent remain unknown. Some clues suggesting possible mechanisms are afforded by the recorded relationship of acute hemorrhagic encephalitis with upper respiratory infections,[2–4] viral infections,[5,6] postvaccinial states,[7,25] drug intoxications,[9–12] and allergic responses.[13] Information concerning the clinical course of the disease is also limited, since the diagnosis has only been confirmed at postmortem examination. As a result of inability to recognize nonfatal cases, this condition has been assumed to invariably produce severe involvement and to terminate fatally.

Five cases of acute hemorrhagic encephalitis were observed at Ullevaal Hospital, Oslo, between December 1953 and June 1954. The diagnoses were established by craniotomy and cerebral biopsy. The survival of two of these cases indicates the necessity of altering the clinical concept of the disease and of investigating the nature of possible residuals. The series as a whole also provided a basis for a reevaluation of clinicopathologic correlations and the possible etiologic factors responsible for acute hemorrhagic encephalitis.

PRESENTATION OF MATERIAL

Clinical findings. This series consisted of three males and two females ranging in age from 31 to 51 years. In most cases prodromata of headache or temperature elevation preceded any neurologic symptomatology. In two cases a productive cough indicated a preceding upper respiratory infection. Symptoms of nervous system involvement then appeared and were often localizing. The findings most commonly noted were hemiparesis and stupor. Hemihypesthesia, quadriplegia, central facial palsy, papilledema, nuchal rigidity, confusion, disorientation, hallucinations, diplopia, and dysphasia were less frequently observed. The frequency

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TABLE 1
FINDINGS IN ACUTE HEMORRHAGIC ENCEPHALITIS (5 CASES)

	Case 1	*2*	*3*	*4*	*5*	*Total*
Prodromata:						
Cough		X	X			2
Fever		X	X	X		3
Headache		X	X	X		3
Neurologic findings:						
Hemiparesis	X	X	X	X		4
Hemihypesthesia	X					1
Quadriplegia	X					1
Paresis of VII					X	1
Papilledema		X		X	X	3
Nuchal rigidity			X			1
Confusion			X		X	2
Disorientation				X		1
Stupor	X	X	X	X	X	5
Dysphasia					X	1
Diplopia				X		1
Hallucinations					X	1
Laboratory findings:						
Cerebrospinal fluid pleocytosis			X		X	2
Leukocytosis	X	X	X	X		4
Elevated sedimentation rate	X	X	X	X	X	5
Abnormal electroencephalogram		X			X	2
Abnormal angiogram		X	X	X	X	4
Biopsy diagnosis		X	X	X	X	4
Postmortem confirmation	X	X	X			3

of neurologic findings is summarized in table 1.

Laboratory findings. The results of laboratory studies were rather inconstant (table 1). In three cases the cerebrospinal fluid cell count was within normal limits, while two cases exhibited a pleocytosis of 106 and 1,100 cells. The spinal fluid protein was elevated to 308 mg. per cent in only a single case. Four of the five patients presented a leukocytosis of between 11,300 and 21,700 white blood cells per cu. mm. All cases exhibited an elevated sedimentation rate.

Angiography. The angiographic findings often suggested a space-occupying lesion. In three cases the involved hemisphere was sufficiently edematous to produce a prominent displacement of the anterior cerebral artery and thereby suggest an expanding intracranial lesion (figure 1). In another case one middle cerebral artery was slightly elevated.

Electroencephalography. Abnormalities in the electroencephalogram in two cases were manifested by continuous delta activity or abnormal potentials.

Hospital course and follow-up. The focal cerebral symptomatology together with evidence of increased intracranial pressure and angiographic abnormalities led to surgical procedures in all five cases. Craniotomy and cerebral biopsy were performed in the four cases which angiographically exhibited displaced vessels. The brain appeared softened and hemorrhagic, but no expanding lesions were located. The suggestion of brainstem involvement by quadriplegia, together with sensory findings in the

FIG. 1. Displacement of the anterior cerebral artery to the left (*case 4*).

fifth case, led to an exploration of the posterior fossa which failed to demonstrate any abnormality.

Three patients expired during the course of the acute disease and two patients survived. One surviving patient now presents only an incomplete left-sided hemianopia despite his early hemiparesis, diplopia, disorientation, and stupor. The second survivor exhibited little improvement following the acute stage of illness. Progressive mental reduction, disorientation, and confusion still necessitate institutionalization.

Biopsy material. In four of the five patients in this series, several small fragments of cerebral parenchyma were removed for biopsy and were studied with hematoxylin and eosin, Weil, Nissl, and Bodian stains. The pathologic alterations varied considerably from patient to patient and even from area to area in the same specimen; however, some features were common to all cases. Slight demyelination was constantly observed, as was diffuse scattering of polymorphonuclear cells throughout the cerebral white matter. Varying numbers of mononuclear cells were also present in each specimen. Perivascular cuffing was generally absent, although some perivascular arrangements of polymorphonuclear cells were present in one case. The surgical procedure resulted in extravasation of moderate amounts of blood; however, additional areas of hemorrhage which appeared unrelated to surgical trauma were present in three cases. Necrosis was absent in all sections examined.

Postmortem examination. Gross examination of the three fatal cases revealed congestion of the meningeal vessels accompanied by scattered areas of subarachnoid bleeding. Parenchymal edema was marked and often asymmetric. In two cases one cerebral hemisphere was sufficiently enlarged to produce herniation of the cingulate gyrus across the midline and a consequent sharp line of indentation of the tissue at the lower margin of the falx cerebri. Section revealed softening of the white matter of the involved cerebral hemisphere and areas of hemorrhage as well as zones of gray discoloration suggestive of demyelination (figures 2 and 3). In one case widespread cerebellar and dorsal pontine hemorrhages accompanied the cerebral involvement.

Microscopic examination revealed hyperemia of the meningeal vessels, extravasation of red blood cells into the subarachnoid space, and scattered inflammatory cells in the meningeal connective tissue. In two cases clinically characterized by an acute course, the cells were predominantly polymorphonuclear, while in the third more chronic case the meningeal infiltrate consisted

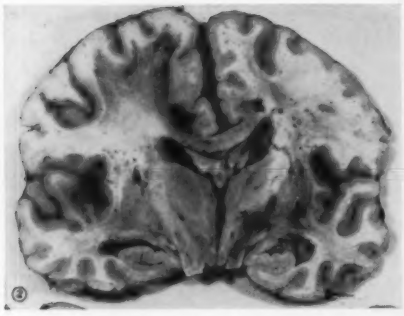

FIG. 2. Small hemorrhagic areas are scattered throughout the cerebral white matter, basal nuclei, and thalamus. The right cerebral hemisphere is enlarged resulting in displacement of the ventricles across the midline (*case 2*).

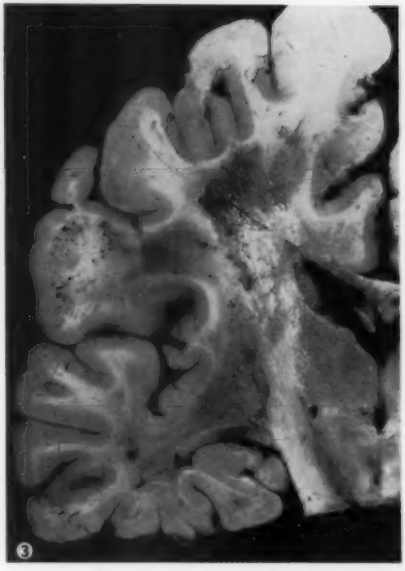

FIG. 3. The deeper layers of the cerebral white matter exhibit softening and gray discoloration. Small hemorrhages are scattered throughout the white matter (*case 1*).

primarily of plasma cells. The cerebral parenchyma exhibited extravasations of blood varying from small ring-and-ball hemorrhages to larger aggregates of red blood cells. Polymorphonuclear cells were scattered diffusely through the involved parenchyma, and perivascular cuffing with these cells was prominent in one case (figure 4). Marked demyelination involving the centrum semiovale together with deeper portions of the convolutional white matter was present in all cases. Both myelin and axis cylinders were destroyed in the demyelinating process. The more superficial white matter along with the U fibers was generally preserved (figure 5). Numerous gemistocytic astrocytes and oligodendrogliocytes were present in the demyelinated areas in one case. In some locations the white matter was fragmented and infiltrated by phagocytes (figure 6). Less severe demyelination and glial proliferation were present in the basal nuclei and contralateral cerebral hemisphere in one case and the cerebellum and dorsal pons in another. Many cortical neurons in the involved hemisphere exhibited chromatolysis and swelling. The parenchymal vessels were congested and often exhibited endothelial proliferation. In one case the involved white matter contained large numbers of distended and thrombosed vessels.

DISCUSSION

Accounts in the literature have led to the impression that acute hemorrhagic encephalitis is almost invariably fatal. Only Oppenheim[14] described surviving cases, but his report was not accompanied by histologic confirmation. The use of cerebral biopsy has allowed the diagnosis of two nonfatal cases of this condition in the five cases reported. It then appears likely that surviving cases

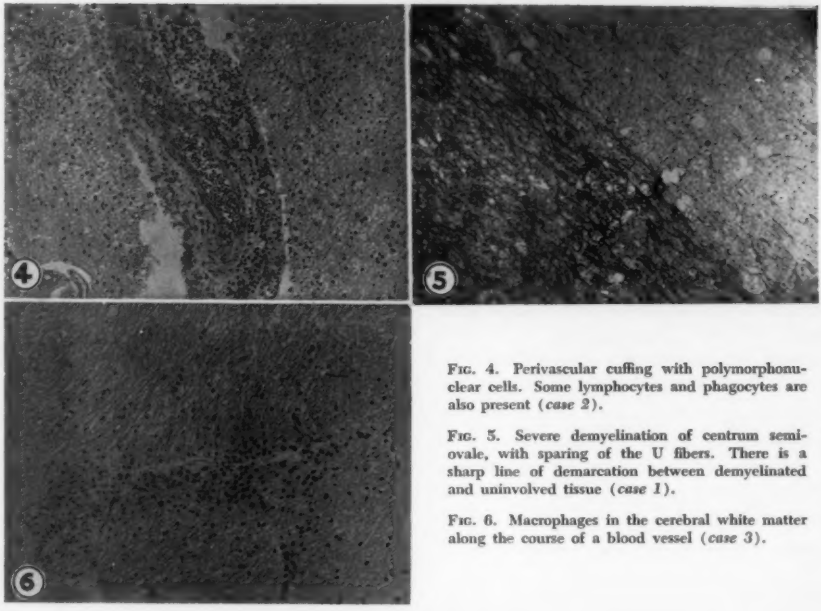

FIG. 4. Perivascular cuffing with polymorphonuclear cells. Some lymphocytes and phagocytes are also present (*case 2*).

FIG. 5. Severe demyelination of centrum semiovale, with sparing of the U fibers. There is a sharp line of demarcation between demyelinated and uninvolved tissue (*case 1*).

FIG. 6. Macrophages in the cerebral white matter along the course of a blood vessel (*case 3*).

may be more common but remain clinically unrecognized because of lack of sufficient diagnostic criteria short of surgical procedures. This study has demonstrated that complete recovery may occur or that severe and longstanding residuals may remain. It is also likely that a number of other cases may fall between these two extremes. Even recognizing that nonfatal cases of acute hemorrhagic encephalitis may occur, the diagnosis remains difficult to establish. The commonly asymmetric involvement has often led to a diagnosis of intracranial neoplasm, abscess, hemorrhage, or infarction. As observed in this series, evidence of increased intracranial pressure together with angiographic alterations strongly suggests the erroneous diagnosis of a space-occupying process. In other cases sudden onset with localizing findings has suggested a cerebrovascular accident. As a result of the similarity of the symptoms of acute hemorrhagic encephalitis to other conditions, the diagnosis can only be established ante mortem by means of cerebral biopsy.

In general, the pathologically more extensive lesions may be well correlated with the clinical findings. However, the total symptomatology is not always reflected by the location of the pathologic process. The damage may be widespread even though the clinical findings suggest only a localized process, since the less severely involved areas may still be capable of maintaining clinically normal function. Contrariwise even extensive pathologic changes may not be reflected in the clinical symptomatology. This was well demonstrated by the single case in this series in which brainstem symptoms

led to the posterior fossa exploration. However, surgery and postmortem examination failed to demonstrate any pathologic involvement in this area. In a second case the cerebellum and pons were severely involved, although this alteration was not suggested in the clinical findings.

Variations in the basic pathologic picture of acute hemorrhagic encephalitis have been described by Hurst,[8] Baker,[15] Adams and his associates,[16] and a number of other investigators.[2,4,10,17–20,33] However, all reported cases exhibited the common feature of varying degrees of hemorrhagic involvement of the cerebral white matter, generally accompanied by a destructive and inflammatory process. On a purely pathologic basis there is little evidence to assume that all these cases represent separate entities, since they present variations of a similar histologic picture. However, the ability of the brain to react in a limited number of ways does allow the possibility of more than a single agent producing a similar picture. Evidence that more than one factor may be at work is afforded by a number of studies. Baker and Buggs,[5] as well as Margulis and his associates,[6] were able to isolate a filterable virus from their cases. In other reports a viral etiology has been suggested by the presence of intracellular inclusion bodies.[7,21–24] Still other studies have strongly suggested an allergic mechanism. Such a mechanism is supported by investigations in which encephalomyelitis resembling acute hemorrhagic encephalitis has been produced in experimental animals by injection of vaccine virus,[25] horse serum,[26,27] or heterologous brain tissue.[28–32]

This investigation cannot adequately elucidate the mechanism responsible for the production of acute hemorrhagic encephalitis. However, five histologically verified cases appeared over the relatively short span of seven months, while no such cases were observed in the preceding two years of operation of the neuropathology service. This concentration of cases is consistent with the mode of action of either a toxic or infectious agent.

SUMMARY

1. The symptoms of acute hemorrhagic encephalitis may be sufficiently localized to suggest a diagnosis of intracranial neoplasm, cerebral abscess, or cerebrovascular accident. The correct diagnosis has only been established thus far by biopsy or postmortem examination.

2. Five cases are reviewed which presented the characteristic histologic appearance of this disorder.

3. The survival of two of the five pathologically verified cases demonstrates that this condition is not necessarily fatal and suggests that the disease is more common than previously considered.

4. Acute hemorrhagic encephalitis has previously been demonstrated to occur in conjunction with viral infection, allergic reaction, and intoxication. The occurrence of the cases in this series during a brief seven month period suggests the possibility of a toxic or infectious etiology.

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CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Charles D. Aring, M.D. and Paul Wozencraft, M.D.*

CASE PRESENTATION

A 58 year old colored construction worker was brought to the hospital at 2 a.m. on February 20, 1955, with left-sided paralysis. He died 36 hours later. One week before admission he had experienced generalized weakness, malaise, and cough, as well as local weakness of the left lower extremity which forced the patient to quit work. Three days later penicillin was administered when a physician found a fever of 101° F. Weakness of the left leg increased and was accompanied by weakness of the left upper extremity in the days following. He complained of impaired vision. It was said that complete left-sided paralysis supervened during the evening of February 19.

The patient had been treated for heart trouble by a physician for a year. About four months prior to admission he was beaten about the head and lost consciousness for an hour. He recovered from this episode and returned to work.

On the ward the patient appeared alert, but he misinterpreted requests at times. He would not relate a consistent story; he said he had "the tb." His speech was slurred. His temperature was 101.4° F. rectally, pulse 64, respirations 24, and blood pressure 180/100. The left pupil was round and larger than the right, which was elliptical; both reacted sluggishly to light. Grade II arteriosclerotic changes were seen in the left ocular fundus and the disk was normal. The right fundus was not seen. Vision was grossly impaired. Movement of the eyes to the right could not be elicited. Swallowing was normal. Resistance of the neck to flexion was encountered but the patient would or could not relax. He could or would not protrude his tongue much. He moved his right limbs well; the left upper extremity was completely paralyzed and the left lower was moved weakly; the lower portion of the left side of the face was weak. Tonus was reduced in the left limbs.

He appeared to appreciate pinprick less well in the left limbs than in the right. All of the deep reflexes were hypoactive. The abdominal skin reflexes and ankle jerks could not be elicited. The left plantar response was less clearly evoked than the right, which was flexor.

The lung fields were clear, except for the right paraspinal area where percussion dullness, increased breath sounds, and moist rales were present. The heart was enlarged to the left and the rhythm was regular. A soft apical systolic murmur was heard. There was no cyanosis or edema. Examination of the abdomen, rectum, and genitals disclosed normal findings.

The hemoglobin was 12 gm. per cent and the white cell count 11,700, with 80 per cent neutrophils. The urine showed an occasional white cell in the sediment. Purulent, blood-stained sputum showed gram positive diplococci in the stained smear; acid-fast stains were negative. Chemical studies of the blood showed: blood urea nitrogen, 21; sugar 308 mg. per cent; CO_2, 29; chloride 97; sodium 132; potassium 4.4 mEq./L.; pH 7.44. The record does not indicate whether or not the sugar was a fasting value. Premature auricular contractions were evident on an electrocardiogram.

Lumbar puncture was performed immediately at the time of admission to the hospital. The patient was coughing and struggling, and the tap was considered traumatic. After the first few bloody drops the fluid was clear. The initial pressure was 260 mm. of water, and

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the final pressure 230 mm. after the removal of 3 cc. The fluid contained 500 red cells and 30 white cells per cmm., with 80 per cent lymphocytes, 20 per cent neutrophils; total protein was 84 mg. per cent. Another tap was done on the following day with better relaxation. The pressure was 170 mm. and the fluid was described as ground glass in appearance. It contained 120 red cells and 440 white cells per cmm., of which 70 per cent were neutrophils and 30 per cent lymphocytes. Total protein was 60 mg. per cent and the sugar 85 mg. per cent. A Wassermann test and gold curve were negative. A smear of the sediment was negative for acid-fast organisms.

Roentgen examination of the chest showed increased transverse diameter of the heart and prominence of the aorta. An area of infiltrate was present in the right lower lung field. Skull films showed no fracture; the pineal gland was not calcified. The glomus of the choroid plexus contained calcium and did not appear displaced.

About four hours after the patient reached the hospital he was having Cheyne-Stokes respiration. The blood pressure was 180/104. Conjugate deviation of the eyes to the right was noted. Plantar stimulation resulted in withdrawal of the limb, more briskly on the right. The patient was restless and forcefully pulled out the Foley catheter twice.

Fluids and penicillin were administered. Early in the morning of February 21 there were repeated left-sided convulsions in which the eyes deviated to the left. The seizures abated after the administration of sodium Amytal; Cheyne-Stokes respiration remained. Later in the morning the convulsions recurred and became almost continuous despite sedation. The temperature reached 104° F. and the neck was described as stiff. He was found pulseless at 2:15 p.m. on February 21.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES D. ARING: We are considering the problem of a 58 year old man who suffered a progressive one-sided weakness over a period of eight or nine days until his death. The protocol suggests that a diagnostic consideration could run the gamut of etiologies, except for congenital, nutritional, and perhaps neoplastic. Inflammation is surely a factor, as may be degenerative change, circulatory disturbance, or a physical agent (trauma); there is meager evidence of disturbance of metabolism in the elevated blood sugar.

There are a few of the findings about which I'd like to comment as an aid to diagnosis. Perhaps this patient suffered more from delirium than the protocol indicates. We have a note of slurred speech, of an inability or unwillingness to protrude the tongue, to relax, or to move the eyes toward the right at the early examination, all perhaps indicators of partial loss of consciousness. The main neurologic help that I get from the protocol is the unmistakable evidence of progression of the disorder. It seems clear that the left limbs weakened progressively from the onset on about February 13 to the hemiplegia of February 19; his death coming as it did so soon after onset points away from the usual, if a diagnosis of stroke is considered. Then there is the history of repeated Jacksonian seizures becoming status epilepticus, that is repeated seizures without return of consciousness between attacks, this during the final ten or 12 hours of life. If anything is needed to tell us that we are dealing with a dynamic rather than a static lesion, the Jacksonian seizures are it. So it appears that we are dealing with a neurologic emergency, wherein accurate and repeated neurologic examinations are imperative if a result other than lethal is to be attained.

Obviously this lesion was localized to the right side of the brain; I am going to pass over any enumeration of the signs that point to this, since they are well known. I want to comment on the deviation of the eyes that occurred four hours after he got to the ward. I believe that this deviation to the right indicated an imbalance between eye-turning centers, those of the left cerebrum being relatively unopposed. Then with the Jacksonian convulsions involving the left limbs, the eyes deviated toward the left, indicating imbalance in the other direction; during this neuronal storm, in contradistinction to what had been the case before, the right brain takes precedence over the left. Again the inference derived should be that we deal with an active lesion and also that the lesion does not destroy the involved cen-

ters, else it would be impossible to explain this shifting of the eyes back and forth.

Regrettably, there is but a single description of the pupils which was made at a time when the patient was first seen. We are told that "the left pupil was round and larger than the right which was elliptical; both reacted sluggishly to light." Particularly for the benefit of the students, I want to go into a short discourse about the changing pupils that result from a wide variety of supratentorial mass lesions. In this situation the behavior of the pupils provides an indicator of changes occurring at the base of the brain; these are predicated on trouble in the third nerve.[1] When this occurs the first thing that happens is an ipsilateral constriction of the pupil, and this is quite rapidly followed by its dilatation. The contralateral pupil is not affected until signs are pronounced on the ipsilateral side. If both pupils are fully dilated and fixed, then look for involuntary ocular movements. The eye on the affected side will be stationary, while the opposite may still be roving. In other words, in the later stages of third nerve dysfunction caused acutely, the somatic motor fibers are the last to be affected. If decompression be effected, the pupilloconstrictor fibers recover rapidly. Accurate and repeated examinations of the pupils are imperative in a case such as this, or in any case where there is a mass lesion above the cerebellar tentorium. Whether or not pupillary signs occur depends on the rate of increase of the mass lesion and the distortion of the third nerve. Since we have no serial pupillary observations in this patient, this information isn't immediately useful, but will be before too long in a hospital such as this.

Now a word about the single blood sugar determination of 308 mg. per cent. We are not told whether or not this test was a fasting one; we have no idea about the relationship of this test to the administration of glucose, if any. I am going to pass over these points since I can't do much with them, and go on to a word about the hyperglycemia which sometimes occurs with relatively acute neurologic lesions. This is a well known occurrence; we don't see it often, but we see it with enough frequency not to become overwhelmed when we find it. It is not known why it happens, but we believe it indicates some involvement of diencephalic centers whether by direction or indirection. In early stroke and with other cerebral lesions where there is an increase of the blood sugar, it isn't advisable to administer insulin since this process usually rights itself reasonably promptly, and to add insulin shock to the problems with which you are already dealing is not helpful.

In considering the nature of the lesion, I think of circulatory, inflammatory, and traumatic etiology. We will take the most common first, the vascular; a 58 year old Negro with established hypertension, rumored heart trouble of one year's standing and a few signs of it now, and grade II arteriosclerotic changes in the retina is a reasonably good candidate for a stroke. It is some such combination as this that frequently lowers our guard and leads us away from one of the main tenets of neurologic diagnosis, namely, that of striving to make a diagnosis of a relievable lesion. It is apparent that this man might have had any of the ordinary strokes; evidence may be marshalled from the protocol for either hemorrhagic or nonhemorrhagic stroke. Time is not available for discussing the evidence for these diagnoses; most of you are quite aware of the usual signs. But for reasons already mentioned, as well as from habit, I am going to strive in this instance for the diagnosis of a relievable lesion. I believe that we are dealing with a dynamic rather than a static problem; in this case there is other evidence, namely, that of infection and the trauma.

There is considerable evidence of inflammation in the protocol to lead us to consider this as the etiologic factor. The patient had fever; he had been given penicillin before entering the hospital, to say nothing about

after his admission here. He had a lung lesion which produced gram-positive diplococci in purulent, blood-stained sputum. We know that infections readily reach the brain from the lung, and it appears that infection was being looked for in the cerebrospinal fluid. One might suspect tuberculous meningitis or brain abscess under the circumstances. I'll consider the cerebrospinal fluid in a moment, but again I would call your attention to the evidence, such as it is, that this disease was not destroying brain so much as interfering with its function.

As far as trauma is concerned, there is almost casual mention of severe injury to the head four months before death. There is no question in my mind that the entire neurologic picture could have been the result of a subdural hematoma. He was of the sex, the socio-economic group, and in an occupation subject to trauma, and it would have been remarkable if he had not been injured more than once, if we don't care to blame the old trauma for the present syndrome. The cerebrospinal fluid findings might be considered to be against the diagnosis of subdural hemorrhage.

Perhaps the spinal punctures might as well have been omitted for the help that we get from them, since several of the measurements or analyses concerning the cerebrospinal fluid might reasonably be questioned. There are significant omissions in the analyses of both of these fluids. Let us admit for the sake of discussion that these are valid differential cell counts on this man's cerebrospinal fluid, in other words that the fluids were stained and that careful differential cell counts had been made on them. What then can we make of these results? Analogous cellular findings have been observed on occasion in the cerebrospinal fluids in subdural and in intracerebral hemorrhage, and they have been explained as aseptic meningeal reaction to subarachnoid blood. If the cellular content of the cerebrospinal fluid is stained and careful differential counts made in subarachnoid hemorrhage, the leukocyte reaction increases progressively until about the third day after bleeding, but practically never to the intensity of that seen in acute bacterial meningitis. However, on rare occasions the meningeal reaction may be intense.[2]

In conclusion then, the few findings culled from the protocol indicate that the lesion was dynamic and relatively nondestructive of brain tissue, favoring a diagnosis of subdural hemorrhage. I have given reasons why the usual stroke is unlikely. As a choice between subdural hemorrhage and cerebral abscess, I prefer the former. There are evidences that the lesion was a surface one and did not destroy cerebral centers, which describes subdural hematoma much better than it does cerebral abscess, at least early in its course. The cerebrospinal fluid findings are not unlike those that have been recorded sometimes in subdural hemorrhage.[2] In any case where this diagnosis is suspected, as I now suspect it, those findings casting doubt on the diagnosis of subdural hematoma are to be discounted, for there is no other reasonable procedure by which we can keep these patients out of the hands of the pathologists. I know of no other way of reducing this number short of giving this diagnosis its intense moment of clear, cool thought in any patient with cerebral signs, particularly in those with a so-called stroke, and in doing more bilateral exploratory burr holes. This I would recommend in a case such as this.

I think, in addition, that this patient was likely to have had bronchopneumonia, and there is evidence of hypertensive cardiovascular disease.

DR. DAVID BLANKENHORN: Twenty-six students attended the morning conference. It was the opinion of 21 that a brain abscess was present; the majority felt it was secondary to pulmonary suppuration; three believed that a subdural hematoma was operating; one felt that the diagnosis was a primary tumor of the brain; another made the diagnosis of tuberculous meningitis.

DR. RICHARD VILTER: Was there a neurosurgical opinion?

DR. HOWARD MC WHORTER: The last note in the chart records that a neurosurgeon was called shortly before death, but the call did not arrive in time.

DR. DAVID BLANKENHORN: Was there a report in the chart about cerebrospinal fluid cultures?

DR. MC WHORTER: No.

DR. M. A. BLANKENHORN: I would anticipate, Dr. Aring, that the blood for sugar determination was drawn, as it often is, to aid in interpreting the cerebrospinal fluid sugar, and so it may be drawn immediately after the tap is done without regard to the fasting state. I think the record many times fails to make that direct statement.

DR. ARING: In this case, then, would you think that the cerebrospinal fluid sugar of 85 mg. per cent was relatively low?

DR. M. A. BLANKENHORN: No, I would not.

DR. ARING: You don't think it reflects the blood sugar that closely?

DR. M. A. BLANKENHORN: I wouldn't think it would reflect a blood sugar change that might be of short duration, but it might if a patient were habitually hyperglycemic.

STUDENT: I'd like to ask Dr. Aring how much importance he attaches to the head injury that the patient received four months previously?

DR. ARING: If it was a hematoma in this case, it could have been of that duration. If so, I don't know how to explain the cerebrospinal fluid findings. As indicated in the record of the cerebrospinal fluid, I relied on there having been some blood therein to explain the aseptic meningeal reaction. It is possible – certainly we have seen it happen – that people harbor subdural hemorrhages for weeks or months, getting along in a reasonably effective fashion, and then decompensate for reasons that we don't understand.

DR. M. A. BLANKENHORN: Would you qualify the term, "decompensate?"

DR. ARING: I use it to cover lack of knowledge. We know that some people get along reasonably well for long periods of time with mass lesions within the skull, particularly subdural hematoma, but there comes a time for reasons that are not particularly clear, perhaps the occurrence of supervening infection or other stress, when something disequilibrates intracranially and the signs become more obvious to the patient and to those who finally bring him to the doctor or hospital; this is what I meant by decompensation; disequilibration would be a synonym equally vague.

PATHOLOGIC DISCUSSION

DR. PAUL WOZENCRAFT: This patient had cardiovascular disease; the heart was enlarged and weighed 630 gm. There was an old scar in the septum that measured 10 by 1 cm. There was minimal coronary atherosclerosis. The right lung weighed 735 gm. and the left 460 gm.; the apex of the right lower lobe was firm and without crepitance. Microscopic sections taken from this area showed lobular pneumonia and beginning organization.

At the autopsy table, the skull was opened with the dura reflected. In the right subdural space we encountered a large mass of clotted blood, partially organized. The right cerebral hemisphere was displaced markedly to the left. The organizing subdural membranes of this massive subdural hematoma extended from the frontal pole to the occipital pole, and from the superior longitudinal sinus mesially to the first temporal convolution on the right, laterally. In addition to the clot, there was a large amount of bloody fluid in the subdural space enclosed in the false membrane. The brain weighed 1,275 gm. The gyri were flattened and the sulci narrowed in the entire right cerebral hemisphere. The right cingulate gyrus was herniated beneath the falx, and there was an uncal herniation on the right through the tentorium measuring 4 cm. in width.

We felt that things were explained reasonably well at the time of autopsy. However, microscopic sections of the subdural

hematoma and the organizing membrane showed a great many neutrophils and some evidence of necrosis. It is difficult to explain these findings except on the basis of an infection of some sort, although cultures of the content of the subdural fluid and a blood culture done after death showed no growth. Cultures of the cerebrospinal fluids that were taken during life (and reported on after death) were sterile.

A microscopic preparation of the brain and leptomeninges immediately beneath the subdural hematoma showed a rather dense neutrophilic reaction in the leptomeninges spreading into the sulci. I believe that this also represented infection (meningitis). This reaction was not generalized throughout the leptomeninges and was more intense in the area beneath the subdural mass; there were some microscopic preparations from the leptomeninges overlying the right hemisphere where we did not see it. But we also found this inflammatory process in the leptomeninges at some distance, for example over the cerebellum. There was conspicuous hyalin arteriosclerosis of the small vessels in microscopic sections from various parts of the cerebral hemispheres.

CLINICAL DIAGNOSIS

Possible tuberculous meningitis, or subdural hematoma, or empyema. Bronchopneumonia, right lower lobe. Hypertensive cardiovascular disease.

DR. ARING'S DIAGNOSIS

Subdural hematoma, right. Lobular pneumonia, right lower lobe. Hypertensive cardiovascular disease.

PATHOLOGIC DIAGNOSIS

Subdural hematoma, right. Lobular pneumonia, right lower lobe. Cardiac hypertrophy of the hypertensive type.

DR. DANIEL OSHER: Were there red blood cells in the leptomeninges as well as neutrophils?

DR. WOZENCRAFT: In the leptomeninges I think the reaction was more neutrophilic than hemorrhagic, but the causative factor of this inflammation was never demonstrated satisfactorily. Postmortem cultures taken from both the subarachnoid and subdural regions gave no growth.

DR. EDWARD GALL: Were there organisms demonstrable in the sections taken from the brain and meninges?

DR. WOZENCRAFT: No.

DR. M, A. BLANKENHORN: Of how long duration was the pneumonia?

DR. WOZENCRAFT: I think it had been there for a while, because there are some areas where it was beginning to show organization.

DR. M. A. BLANKENHORN: Therefore, it preceded the convulsive state. Is it imperative that this cellular infiltration in the walls of the subdural hematoma be infectious?

DR. WOZENCRAFT: I don't know that it's imperative, but I feel a bit uncomfortable about any other explanation, with that many neutrophils as densely packed together and showing necrosis.

DR. GALL: We have no means of explanation other than infection. Do you suppose the hematoma was of four months' duration?

DR. WOZENCRAFT: I think it could have been. There was considerable organization in the walls, as well as granulation tissue.

DR. GALL: Do you have a comment to make, Dr. Aring?

DR. ARING: In one of the cerebrospinal fluids taken from reported cases of subdural hemorrhage,[2] one cell count reached 6,850 polymorphonuclear leukocytes per cu. mm. That seems like a good deal, and no infection was postulated. This particular patient recovered after the evacuation of the hemorrhage.

DR. HERBERT BRAUNSTEIN: But in that case there was almost an equal number of red cells (5,050 per c. mm.).

DR. ARING: I don't see that the cellular ratios were much different in our case. In the first tap there was reported 500 red blood cells and 30 white blood cells (20 per cent neutrophils); and in the second cerebrospinal fluid, 120 red blood cells and

440 white blood cells (70 per cent neutrophils).

DR. VILTER: May I ask Dr. Aring when he would have called in a neurosurgeon?

DR. ARING: The sooner the better; in retrospect, as soon as I saw the patient. I cannot say without having seen the patient how soon I would have entertained the idea that this man had a subdural hemorrhage. I certainly would have been more than suspicious if I had had a firm story of trauma; sometimes such information is discovered late, perhaps when the patient is dying or even after he is dead.

DR. WOZENCRAFT: The history of trauma was obtained at the time of admission.

DR. ARING: I don't know how I can answer Dr. Vilter's question objectively. I believe I would have been suspicious at first, because I give subdural hemorrhage some thought in every case where there is hemiparesis. I don't know any other way of making the diagnosis of subdural hemorrhage with some consistency.

STUDENT: You mean you would have suggested surgery if you had seen this man?

DR. ARING: Not only do I usually suggest surgery, but often I have wished that we had the instruments on the wards so that we wouldn't have to go through the misery of calling out an operating staff. Subdural exploration is a simple procedure except for the arrangements that have to be made before the patient can be got to the operating room. I am of the opinion, in the current antibiotic era, that an able physician could explore the subdural spaces; also I am quite sure that most surgeons would object to such a procedure.

DR. OSHER: There are two points I want to make in regard to this case. A history of trauma is not required and should not be worried about if it cannot be obtained, and the story of the developing illness is crucial in this patient. The factor of progression was essential in making the diagnosis of a subdural hematoma here, and, once suspected, this is the indication for exploration.

DR. SAMUEL A. TRUFANT: Progression over this period of time is strong evidence of some sort of a mass lesion, whether it be subdural hemorrhage, abscess, or tumor.

DR. ARING: I wonder how many subdural hematomas are getting to the pathology department without being suspected these days. We saw one in our brain sectioning session yesterday, in a child one and a half years of age, which presumably had been present since birth. The child had been considered to have had cerebral palsy.

DR. GALL: Dr. Smith, do you have any estimate of that?

DR. JOSEPH SMITH: I believe it is much more common in America than in countries that are not quite so traumatic. I would suspect that in this hospital there are from six to ten in a year.

This seems to me to be a very interesting case in that we are left with the possibility that infection settled in a chronic subdural hematoma and possibly exacerbated it to some extent, a thing which I have never come across before or read about, but which I think did happen in this case. I don't think that I have ever seen so many polymorphonuclear leukocytes in a chronic subdural hematoma before.

DR. ARING: How do you propose that infection got there, if it did?

DR. SMITH: By the bloodstream.

DR. ARING: Do you believe he had a septicemia?

DR. SMITH: Well, he had pneumonia.

STUDENT: What about the calcified glomus of the choroid plexus that was not displaced?

DR. ARING: For those who don't know much about this structure, it is the enlargement of the choroid plexus in the mesial portion of the lateral ventricle. I don't know how much one can rely on displacement of choroid plexus calcifications in localization. Would you have an opinion, Dr. Osher?

DR. OSHER: Calcification in the glomus is often very vague and nebulous, and extends over quite an area in comparison with pin-

eal calcification. It would be of interest to determine if bilateral calcification was present so that one could compare them; the nature of these densities usually is such that that of one side has to be compared with the other.

(Examining the roentgen studies of the skull): There are two very faint calcifications, one a little more distinct than the other; they are approximately in their normal position. There is also a faint calcification of the pineal gland which seems shifted slightly toward the left side, but this latter calcification would have to be studied with stereoscopic views to be sure that this is the pineal gland. From these plates the suggestion is obtained that the choroid plexuses are in their normal positions.

STUDENT: I'd like to ask Dr. Aring if he places much weight on the increased protein in the cerebrospinal fluid?

DR. ARING: No, the protein in the cerebrospinal fluid may or may not be increased in subdural hematoma.

STUDENT: Dr. Aring, would you comment on the fact that the cerebrospinal fluid was not xanthochromic?

DR. ARING: How can you tell that it wasn't? It doesnt' say so in the protocol; this was one of the omissions about which I was complaining when I discussed the cerebrospinal fluids.

DR. MC WHORTER: The record of the cerebrospinal fluid makes no mention about xanthochromia.

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■ In reviewing carefully all the cases that we know of alteration of the posterior columns of the spinal cord, we find that usually an alteration, limited to a small part of the length of these columns, does not affect the voluntary movements, while, on the contrary, there is no case in which an alteration extending a few inches in either the cervical or the dorso-lumbar regions, has not produced a diminution of voluntary movements in either the upper or the lower limbs. When the alteration exists along the cervico-brachial enlargement, the paralysis exists in the upper limbs and not in the lower ones. There are several cases, however, in which an alteration in the cervical region co-existed with a paralysis of the lower limbs, but the cause of this loss of power may be found in other circumstances than the alteration of the posterior columns, as we shall show in a moment.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Transient Glaucoma in Viral Encephalitis with Diencephalic Lesions

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THIS REPORT deals with the simultaneous occurrence of transient glaucoma and viral encephalitis, principally affecting the diencephalon. The concurrence of these conditions may be merely coincidental. However, in view of the recent demonstration that intraocular pressure may be raised by stimulation of the diencephalon[1] and in view of the clinical suggestions that disease of the diencephalon may lead to glaucoma,[2-4] it is possible that glaucoma and encephalitis might be causally related in this case Since no similar case has been found in the literature, it was thought of interest to document these data.

A 62 year old woman was well until 15 days prior to death, when she noted malaise, rectal discomfort, and pain referred to the right hip, shoulder, and subcostal region. The past medical history was noncontributory. Sigmoidoscopy performed six days later revealed no abnormalities. A fever of 102° F. developed the next day and Terramycin was administered. The following day, seven days before death, the patient complained of saliva dripping from the left corner of the mouth and of "puffiness" of the left palm. The latter was objectively observable. The next day the patient was found "preparing food" in her kitchen at 2 a. m. This was the first indication of an abnormal mental state noted by her family and they remarked that her activities seemed aimless. Later that morning she became incontinent of urine and feces, talked incoherently, and when spoken to did not appear to understand.

About noon the same day pain developed in both eyes. The patient's pupils were then observed to be markedly dilated and both corneas were noted to be steamy. The tension was 60 mm. Hg in each eye. Pilocarpine, DFP, and eserine did not affect pupillary size.

About two hours later the first of a series of six generalized seizures occurred, with the head and eyes turning to the left. At this time the spinal fluid was clear, colorless, contained no cells, and was under 140 mm. of water pressure. The total white blood count was 15,000, predominantly polymorphonuclear cells.

The patient was hospitalized five days before death. The temperature was 99° F., respirations 24, pulse 88, and blood pressure 170/70. She was semicomatose, responding only to painful stimuli. There was more movement on the right than left in response to painful stimuli. The head and eyes were usually deviated to the right. There was moderate hypertonus, greater on the right than on the left. The deep tendon reflexes were difficult to obtain in the upper extremities. The left knee jerk was hyperactive, there was a right Babinski sign, and the left plantar response was not normal. The neck was stiff but the Kernig and Brudzinski signs were not elicited. A second spinal tap showed the fluid to be clear and colorless. It contained no cells and 72 mg.

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per cent of protein. The initial pressure was 190 mm. of water.

By this time the pupils were widely dilated and unresponsive to light. The corneas were so steamy that the fundi could not be seen. The tension was 56 mm. Hg in each eye.

The patient's course in the hospital was progressively downhill and marked by recurrent convulsions and increasing coma. On the day after admission, at which time the patient was still being treated with pilocarpine, the corneas became somewhat transparent. The fundi were then observed to be normal. Two days after admission the ocular tension was 17 mm. Hg in both eyes.

A ventriculogram was performed and found to be within normal limits. An electroencephalogram showed a diffuse abnormality. The blood urea was 8 mg. per cent, blood sugar 100 mg. per cent, blood and cerebrospinal fluid Wassermann negative, and the colloidal gold curve flat. The temperature varied between 101° and 102° F. Death occurred on the fifth hospital day.

Autopsy revealed multiple pulmonary emboli, apparently arising in the pelvic veins and causing extensive pulmonary infarction. There were multiple small hemorrhages in the peritoneum, endocardium, and the gastrointestinal, urinary, and respiratory tracts. A duodenal ulceration was present, and the colon contained numerous diverticuli. Permission to examine the eyes was not granted.

Grossly the brain appeared small. Defects due to needle aspiration were apparent on the surface, and a small hemorrhage was present in the left caudate nucleus in the course of a needle tract. There were no other gross changes.

Microscopically a moderately severe chronic leptomeningitis was noted, most intense in the hypothalamic area and less marked over the cortex and brainstem. Lymphocytes predominated, with varying number of large mononuclear cells of arachnoid origin present as well.*

Parenchymal lesions of varying character were present throughout the brain. They involved gray and white matter bilaterally, most frequent and intense in the thalamus and hypothalamus, somewhat less marked in the corpus striatum, and still less marked in the cortex, cerebral white matter, midbrain, pons, and medulla. No lesions were found in the cerebellum. The cord was not available for study. The most common lesions were those in which the perivascular spaces were dilated and contained varying numbers of lymphocytes and a few large mononuclear cells. Foci of parenchymal necrosis were also observed, associated with polymorphonuclear cells and a reactive proliferation of microglial cells. These were generally small except in the thalamus, where broad zones of destruction were present. In some of these, groups of neurons were seen undergoing coagulative necrosis without any evidence of accompanying reaction. In other areas such necrotic neurons were surrounded by well circumscribed zones of pallor and rarefaction, while in still other zones the neurons were completely destroyed, the area was rarified, and contained a great many phagocytic cells and moderate numbers of polymorphonuclear cells. These areas resembled zones of encephalomalacia. In other portions of the brain, parenchymal lesions were very much smaller, containing only a few phagocytic cells and very few polymorphonuclear cells. Numerous relatively old ependymal granulations were noted in the lateral and third ventricles and in the aqueduct. Most appeared obsolete. More recent granulations were seen at the inferior angle of the aqueduct, where some of the astrocytes remained hypertrophic.

*In view of these changes, it is noteworthy that no cells were found in the cerebrospinal fluid, a not unusual occurrence in encephalitis.

DISCUSSION

The diagnosis of glaucoma in this case was based on pain in the eyes associated with dilated pupils, steamy corneas, and increased intraocular tension which reached 60 mm. Hg. This ocular hypertension persisted for four days during appropriate treatment, following which these features disappeared.

The diagnosis of viral encephalitis was indicated by the clinical features and by the pathologic findings. A definitive diagnosis of the viral encephalitides is possible only if the virus itself has been isolated and identified or if serologic evidence of the production of specific antibodies has been obtained. This information was not available in the case reported here.

Presumptive evidence suggested that the changes were probably due to the virus of Eastern equine encephalomyelitis. This is probably the most common etiologic agent in viral encephalitis in the New York area. The involvement of both gray and white matter is unlike that in acute disseminated

encephalomyelitis, where the lesions are essentially restricted to the white matter, and unlike that in rabies or in von Economo's encephalitis, where the gray matter is primarily affected. In these latter conditions the structures most severely affected are the medulla and midbrain, respectively. In the case presented here, the most severe lesions were in the thalamus, with less severe and less frequent lesions in the brainstem, cortex, and subcortical white matter. The lesions in herpes and inclusion encephalitis differ in that the most severe lesions involve the cortex and intranuclear inclusions may be found.

Comparable changes are seen in the other members of the arthropod-borne group of viral encephalitides, which includes the equine encephalomyelitides, St. Louis, Japanese B, and a great many others. St. Louis encephalitis is generally less severe. Japanese B encephalitis is often very severe, with necrotizing lesions most frequent in the gray matter and often involving the cerebellum. The latter was unaffected in the case reported here. Western equine encephalomyelitis is similar to the present case, although some reports indicate that one would expect more extensive damage to myelin in otherwise unaffected areas, more frequent hemorrhages, less severe meningitic involvement, and most particularly, a lesser neuronal involvement. Although the distribution and character of the lesions in this case most closely resembled Eastern equine encephalomyelitis, it must be conceded that, in an individual case, such lesions may be caused by one of the other viruses, especially within the group of arthropod-borne diseases.

The diencephalic lesions demonstrated in this case and the theoretical considerations which implicate the diencephalon in the pathogenesis of glaucoma suggest the possibility of a causal relationship between encephalitis and glaucoma.

Diencephalic dysfunction as a cause of glaucoma has been postulated by Magitot,[2,5,6] who raised many questions about glaucoma which are difficult to answer in terms of a simple increase in ocular tension. Many of these questions, Magitot postulated, may be understood by considering glaucoma as a manifestation of a lesion in the intracranial course of the optic nerve. Thus, the atrophy becomes a descending atrophy, while the accompanying diencephalic dysfunction results in vasomotor disturbances which give rise to the major part of the clinical picture. In addition, Magitot considered the disorder of accommodation, tonic pupil, disturbances in lachrymation, and various endocrine changes accompanying glaucoma as suggestive of disease of the diencephalon. He also described emotional lability as part of the syndrome, and thus classified glaucoma as a neuropsychiatric dysfunction. Hess[3] essentially agreed with Magitot in regard to the origin of the optic atrophy in glaucoma. Accepting the diencephalic origin of glaucoma, Cristini[7] treated glaucoma with irradiation to the region of the pituitary. He reported improvement in the visual field in every one of nine cases. In 1946 the same author[8] described reduction of intraocular tension in glaucoma after irradiation of the superior cervical ganglion and medulla. In fact, this investigator proposed such treatment as a therapeutic-diagnostic test for glaucoma, and concluded that this disease is due to autonomic imbalance.

In passing, it may be added that Magitot pointed out that the pupillary dilatation in glaucoma is not due to intraocular hypertension. This contention is supported by the work of Matteucci and Carusi,[9] who raised the intraocular tension in rabbits but failed to find changes in pupillary size.

The occurrence of glaucoma secondary to pituitary-diencephalic dysfunction has also been reported by Zondek and Wolfsohn.[4] These authors examined 22 cases of so-called primary glaucoma for evidence of pituitary-diencephalic dysfunction (for example, carbohydrate and water metabolism, basal metabolic rate, blood cholesterol, phy-

sique, osseous structure of the skull, menstrual history, and weight). Of these 22 cases, 16 were considered to have evidence of pituitary-diencephalic dysfunction. Of these 16, pituitary tumors were demonstrated in six cases, two of whom had acromegalic changes.

These authors suggested two possible mechanisms for production of acute intraocular hypertension: 1) abnormal vascular function manifested either by narrowing of the blood vessels with secondary blocking of Schlemm's canal or abnormal dilatation of the vascular bed accompanied by increased permeability; 2) excessive hydration of the vitreous as a result of antidiuretic hormone abnormalities.

Duke-Elder[10] stressed the primary role of vasomotor and endothelial instability and their relationship to neurovegetative and endocrine imbalance in the pathogenesis of glaucoma. He considered the obstruction to circulation and drainage of the intraocular fluids as an adjuvant factor in its etiology.

This brief review of the clinical literature suggests that diencephalic dysfunction may play a causative role in glaucoma. A more direct demonstration of the relationship was recently shown by von Sallmann and Lowenstein.[1] These investigators observed that the intraocular pressure of the cat can be raised by electric stimulation of appropriate areas of the diencephalon. Stimulation of some points effected a rise in intraocular tension associated with changes in systemic blood pressure, the pupillary size, and nictitating membranes, indicating a diffuse sympathetic discharge. At other points the rise in pressure was associated with contractions of the smooth or striated extraocular muscles. However, stimulation of the dorsal hypothalamus and the ventral part of the thalamus commonly resulted in a rise in intraocular pressure alone.

This demonstration of a rise in intraocular pressure without a generalized sympathetic discharge upon electric stimulation of the diencephalon would seem to place the theory of the neurogenic concept of some forms of glaucoma on a firm basis and to support the clinical deductions already noted. The areas from which von Sallmann and Lowenstein elicited isolated rises in intraocular tension also happen to be the sites of the most intense lesions in our case, lesions which may be considered to be irritative as well as destructive. Thus there are clinical and experimental reasons to suspect that the glaucoma in our case was the result of diencephalic dysfunction secondary to encephalitis.

However, we cannot disregard the fact that glaucoma is not reported in conditions in which hypothalamic involvement is frequent, such as Wernicke's encephalopathy, Schuller-Christian's disease, and indeed in other cases of viral encephalitis in which diencephalic lesions occur. It must also be considered that hypothalamic lesions have not been reported in the brains of patients with glaucoma. While the concurrence of the glaucoma and the hypothalamic lesion reported may be fortuitous, in view of the experimental findings and the clinical theories it is considered of value to report this coincidence in the hope that interest in this specific problem may be stimulated.

SUMMARY

A case is described in which transient, acute glaucoma occurred early in the course of an acute viral encephalitis. The possibility of a causal relationship is suggested in view of the theories of the pathogenesis of acute glaucoma and the demonstration of a rise in intraocular pressure following electric stimulation of the diencephalon of cats.

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■ We have said already that anaesthesia alone – i. e. without a paralysis of voluntary movements – is not a symptom of disease of the spinal cord, or at least of ordinary diseases of the organ, as we have acknowledged that there are two kinds of alterations that might produce a much more marked anaesthesia than a paralysis of voluntary motion, and even, perhaps, diminish voluntary movements almost only on account of the anaesthesia produced. One of these alterations would be an injury or a morbid transformation all along the posterior horns in which the posterior roots pass before going to the other parts of the spinal cord. In such a case there would be anaesthesia on the side where the alteration exists, if it is limited to one side of the cord, and the loss of sensitivity would be localized to those parts which receive their sensitive nerve-fibres from the regions altered; so that, below and above, sensibility might exist. We do not know of a single case of this kind; some, however, may have been observed.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Intracellular Water and Potassium in Periodic Paralysis

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PERIODIC PARALYSIS comprises a syndrome whose clinical features have been often described. These may be summarized briefly as follows: frequent familial incidence, appearance of symptoms in the first two decades of life, episodes of flaccid paralysis involving all or part of limb and trunk musculature and associated with arreflexia and electrical inexcitability, frequent onset of paralytic episodes in the early morning hours of sleep, spontaneous resolution of paralysis within three days after its onset, and complete absence of symptoms in the intervals between attacks.[1–8]

The pathophysiology of this condition has not yet been adequately defined, but the importance of potassium has been clearly indicated by numerous investigators. In 1935 Biemond and Daniels[5] noted a fall in the blood potassium of 4 mg. per cent during an attack of paralysis, and since then similar and more dramatic decreases in blood potassium have been described.[6,8–10] The work of these authors included the study of paralytic attacks artificially induced by varied agents, such as insulin, adrenalin, high carbohydrate intake, and oral administration of large amounts of water, and during all such artificially induced attacks the serum potassium was found to be significantly low. The ability of orally administered potassium chloride to terminate an attack and restore the normal blood level was also clearly demonstrated.

The electrocardiographic findings in a paralytic episode were first completely described by Stewart and co-workers,[11] and these changes have since been correlated with the hypokalemia of other diseases as well. These findings comprise lowering, flattening, or inversion of the T-waves, prolongation of the PR and QT intervals, depression of the RS-T segments, and development of U waves.[12] A review of the literature reveals no ballistocardiographic studies of hypokalemia.

Although the fact of potassium exit from the vascular compartment is now well known, the reservoir into which it disappears has not yet been identified. Gammon and co-workers[10] and Ferrebee and co-workers[13] found no increase in the urinary loss of potassium prior to or during spontaneous episodes of paralysis. Talbott[7] and Danowski and co-workers[14] similarly found no increase in the urinary loss of potassium prior

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to or during attacks induced by the oral administration of large amounts of glucose. In addition, Danowski's group,[14] by means of balance studies demonstrated a shift of potassium from the extracellular into the intracellular phase associated with a falling serum level of potassium, decreasing urinary excretion of potassium, and the development of paralysis. To our knowledge no attempt has been made to demonstrate this increase in intracellular potassium in a more direct manner.

There is a body of data which indicates the importance of metabolic variables other than the serum potassium level. Hypokalemia is a frequent finding in many disease processes and may be induced in normal individuals by the administration of insulin or adrenalin, but in these situations it is seldom accompanied by specific flaccid paralysis. On the other hand, apparently authentic instances of familial periodic paralysis without blood potassium changes have been reported.[15–17] The conclusion is strongly suggested that the contractility of skeletal muscle is not a function of the serum potassium level alone but may also be related to the intramuscular concentration of potassium.

CASE REPORT

A 21 year old white soldier had had 11 episodes of paralysis since the age of 17. Attacks always began in the early morning hours of sleep, lasted one to three days, and resolved in four to five hours, leaving the patient completely asymptomatic. Paralysis varied in intensity, and on five occasions it was complete, involving all the muscles of neck, trunk, and the four limbs. Paralysis always started in the distal muscles and extended proximally. Resolution of paralysis was associated with cramps, stiffness, and soreness in the muscles. Urination and defecation never occurred during an episode of paralysis, although the patient was sometimes uncomfortably aware of bladder distension. He believed that attacks were related to excessive physical or sexual exertion but not to diet. He has sometimes been able to postpone an attack by walking about and vigorously swinging his arms. The medical history otherwise was noncontributory. Careful inquiry revealed no instances of similar episodic paralysis in other members of the family.

Examination during a major episode revealed complete flaccid paralysis of all neck, trunk, and limb muscles, with diminished thoracic respiratory excursions, weak cough, and generalized arreflexia. Limb muscles were unresponsive to electrical stimulation at the motor points, with square wave pulses of 500 millisec. duration and up to 18 milliamp. magnitude. At higher current values there was a slow contraction which could not be adequately studied because of the associated pain. General physical and neurologic examinations were otherwise entirely normal. Following resolution of the attack, physical examination was completely normal.

The following determinations performed in an asymptomatic interval were all normal: complete blood count, routine urinalysis, blood serology, chest film, basal metabolic rate, blood glucose, calcium, inorganic phosphorus, creatinine, total cholesterol and cholesterol esters, eosinophil count, and urinary output of 17-ketosteroids. Urine was negative for ribose according to the method described by Orr and Minot.[17]

The significant data for this report concern the analysis of muscle for potassium, water, and chlorides as described by Porter and co-workers.[18] Two muscle biopsies were taken from corresponding regions in both deltoids, one during the height of an attack of paralysis and the second eight days after recovery from this attack. The biopsies were performed under local anesthesia without infiltration of the muscle, and all gross fatty tissue was removed with scissors at the time of biopsy. The serum potassium and urinary output of potassium were determined daily for seven days before the attack of paralysis, during the attack, and for five days afterward. All potassium determinations in muscle, serum, and urine were performed with the Janke flame photometer which contains an internal lithium standard. Serum chlorides were determined by the Schales method, and muscle chlorides were determined after digestion with nitric acid and silver nitrate by a modification of the Volhard method.

Electroencephalograms, electrocardiograms, and ballistocardiograms were obtained simultaneously on a 6 channel Offner ink writing electroencephalograph before, during, and after this same spontaneous attack of paralysis. Ballistocardiograms were made with a direct pretibial body pickup moving parallel to the longitudinal axis and projecting a beam of light onto a photoelectric cell (Sanborn) which fed into the machine.

The calculated values in table 1 were obtained as described by Porter and co-workers.[18] The Donnan factor used to calculate extracellu-

lar electrolyte concentrations from serum values was 0.96 for potassium and 1.04 for chlorides. This calculation of extracellular muscle water assumes all muscle chloride to be in the extracellular phase.

During the entire period of observation the patient's dietary intake remained normal and constant except for some over-all depression of intake during the episode of paralysis studied. The intake of potassium ion calculated for a single representative day was 88.5 mEq. The patient's weight one week before the paralytic episode was 89.6 kg.

RESULTS

Table 1 summarizes the results of serum and muscle analyses for potassium, chloride, and water. The normal values were obtained by the same technic in the same laboratory from five normal individuals and have been reported elsewhere by Porter and co-workers.[18] The patient's dietary intake was somewhat depressed during the episode of paralysis, but there had been no vomiting and he appeared to be well hydrated clinically. Table 1 shows a fall in the serum potassium to 1.83 mEq./l. during paralysis without significant change in the whole muscle potassium. There was, however, during paralysis an increase of 1.44 l. water per kg. muscle solid, of which 0.73 l. was extracellular and 0.71 l. intracellular. When the potassium is referred to muscle solid it is seen that each kg. of muscle solid received into its intracellular compartment 129 additional mEq. of potassium.

Ballistocardiograms taken before, during, and after the episode of paralysis were within the limits of normal and showed no significant changes in the individual wave patterns.

Electroencephalograms taken before, during, and after the episode of paralysis were normal and alike with respect to amplitude and frequency.

Electrocardiograms showed the following changes during paralysis: depressed RS-T segment, prolonged PR and QT intervals, and broadened, low amplitude T waves. U waves were not prominent in this case.

Urine studies as graphed in figure 1 show that for seven days prior to paralysis on day 7.5, the output of both urine and potassium gradually decreased, falling, in the case of potassium, from 108 mEq. per day to 2.34 mEq. per day. No significant changes in serum potassium occurred during this preparalysis interval. The serum potassium and the urinary output of both water and potassium increased markedly upon the subsidence of paralysis on day 8.5, several hours after the administration of 12.5 gm. of potassium chloride by mouth.

TABLE 1.

MUSCLE AND SERUM VALUES FOR CHLORIDES, WATER, AND POTASSIUM DURING AND AFTER AN EPISODE OF PARALYSIS

	mEq. per L. Serum		*mEq. per Kg. Whole Muscle*		*L. Fluid per Kg. Whole Muscle*			*mEq. per Kg. Muscle Solid*		*mEq. Intracellular K+ per Kg. Muscle Solid*	*mEq. per L. Intracellular Water*	*L. Fluid per Kg. Muscle Solid*		
	K+	*Cl−*	*K+*	*Cl−*	*Total*	*Extracellular Water*	*Intracellular Water*	*K+*	*Cl−*		*K+*	*Total*	*Extracellular Water*	*Intracellular Water*
Symptom Free	4.30	102	86.3	33.2	.745	.314	.431	338	130.5	332	196.5	2.92	1.23	1.69
Paralysis	1.83	115	86.0	43.5	.814	.364	.450	462	235	461	190	4.36	1.96	2.40
Normal Range			91 to 93	27.4 to 35.3	.744 to .774	.251 to .334	.433 to .503	359 to 406	107 to 151		180 to 207	2.90 to 3.42	.979 to 1.44	1.85 to 2.21
Normal Average	4.5	105	91.8	29.7	.765	.280	.484	391	126	384	188	3.26	1.19	2.07

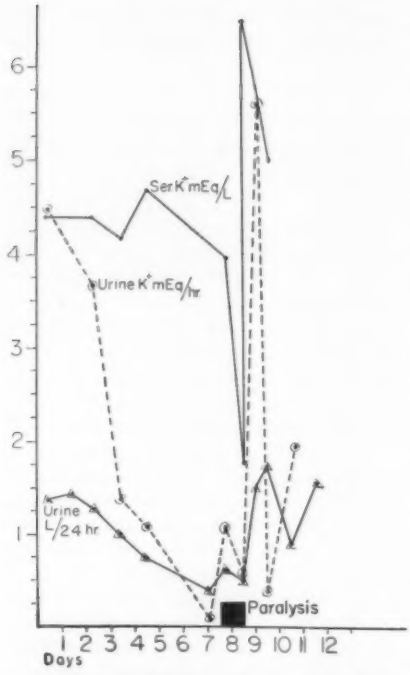

FIG. 1. Serum potassium, urinary output of potassium, and urine volume before, during, and after episode of paralysis.

DISCUSSION

Assuming that 38 kg. of our subject's total 89.6 kg. were muscle, of which 25.5 per cent was muscle solid, one calculates a total muscle solid of 9.7 kg. From the value of 1.44 l. water per kg. muscle solid gained during paralysis the total amount gained is calculated to have been 14 l. This large gain in muscle water was clearly related to the diminished output of urine which existed for six days prior to the onset of paralysis. The maximum amount of water so gained is calculated to have been 6 l., assuming a constant intake and a normal 24 hour output of 1.51 l. as reported six days before the onset of paralysis. A decrease in the amount of water lost by perspiration and a shift of water from non-muscle tissue seem the most likely sources for the remaining gain of 8 l. It is not believed that edema at the biopsy site due to muscle paralysis and vascular stasis made an important contribution to this gain. The deltoid muscle from which the sample for analysis was taken was not in a dependent position, since our subject had remained in a sitting position throughout the paralytic episode. The separation of this muscle water gain into intracellular and extracellular components rests on the assumption that all of the muscle chloride was extracellular. This assumption is probably valid in the case of normal muscle only. Ussing[19] has pointed out that in depolarized muscle the concentration of intracellular chloride given by the Donnan equilibrium becomes a significant factor in the calculation of intracellular water. This means that our calculation of 0.71 l. of water entering the muscle cell during paralysis is probably too low, and the fact of intracellular hydration appears even more prominent. If intracellular hydration of muscle bears a causal relation to individual episodes of paralysis, one should be able to precipitate paralysis in a susceptible subject by means of a high salt and water intake or with pitressin. It seems probable to us that Gammon and co-workers[10] performed this experiment when they precipitated a severe attack of paralysis with large amounts of water administered orally. These authors, however, ascribed the paralysis to loss of potassium by diuresis.

The analysis in our subject revealed a gain of 129 mEq. of intracellular potassium per kg. of muscle solid during paralysis. Insofar as the assumption with regard to the extracellular location of muscle chloride is in error, this calculated value is somewhat lower than the true value. Assuming again a total muscle solid of 9.7 kg., one calculates a total gain in intracellular potassium of 1,250 mEq. With a constant intake of 89 mEq. per day and an output in the urine of 79, 32, 25, and 2 mEq. per day on the four days immediately preceding the paralytic episode, 225 mEq. of potassium could

have been made available to the intracellular muscle compartment. The remaining 1,025 mEq. must have come from other tissues. If it is true that a normal 70 kg. man has 1,200 mEq. of potassium in tissues other than muscle, this constitutes an astonishing shift to muscle of more than two-thirds of our subjects' supply of potassium in other tissues. The marked fall in the urinary output of potassium on the day prior to the onset of paralysis and the fall in the serum level of potassium on the day of paralysis identify the final stages in this shift, but its mechanism remains obscure.

The intracellular concentration of potassium during our subject's episode of paralysis is given in table 1 as 190 mEq./l. and the ratio of the concentrations of intracellular to extracellular potassium is

$$\frac{190}{1.83 \times 0.96} = 109,$$

compared with the normal ratio of

$$\frac{196.5}{4.3 \times 0.96} = 47.7,$$

an increase by a factor greater than two. Although our assumption with regard to the extracellular location of chloride may have resulted in too high a value for our calculated concentration of intracellular potassium during paralysis and consequently too high a value for the ratio, it may be seen to be unlikely that the ratio remained unchanged during paralysis and even more unlikely that it decreased. For the ratio to have remained unchanged the intracellular potassium would have had to decrease to

$$196.5 \times \frac{1.83 \times 0.96}{4.30 \times 0.96} = 84.0 \text{ mEq./l.}$$

Substituting this figure in the equation which relates m = intracellular K^+ in mEq. per l. to n = extracellular Cl^- in mEq. per kg. whole muscle,

$$m = \frac{86 - \frac{1.83 \times 0.96n}{115 \times 1.04}}{0.814 - \frac{n}{115 \times 1.04}}$$

one finds a value for n = 23.3. This means that 43.5 — 23.3 = 20.2 mEq. Cl^- per kg. whole muscle, or almost one-half the total muscle chloride, must have been intracellular in order that a normal potassium ratio might be maintained. Since this high value for the intracellular fraction is most improbable, one may conclude that the potassium ratio did in fact increase during paralysis because of the fall in the concentration of extracellular potassium, although probably by not as much as our figures indicate.

Hodgkin[20] has reviewed those investigations which indicate a relationship between the resting potential difference across nerve and muscle membranes and the ratio of the concentrations of intracellular to extracellular potassium. The exact and general formulation of this relationship is still in question, but experimental observations give considerable support to the statement that the resting membrane potential is an increasing function of the potasium ratio when experimental conditions make the ratio a function of the external potassium concentration alone. If this statement may be applied to human muscle, the analyses in our subject indicate an increase in the resting muscle membrane potential during paralysis. The suggestion follows that this increased resting potential may be directly related to the paralysis, illustrating the activity of the same mechanism whereby anodal polarization raises the threshold of nerve and muscle fibers to electrical stimulation. Intracellular hydration of muscle would therefore have resulted in paralysis in our subject because of the associated shift of potassium from the nonmuscle tissues with ultimate fall in the serum potassium level.

Figure 1 shows that for six days prior to the onset of paralysis the renal excretion of water and potassium continued to fall in the face of a normal serum level of potassium. Paralysis occurred coincident with the fall in serum potassium. The time extent over which these changes occurred suggests some modification of the traditional concepts of this disease.

Our inability to demonstrate clear-cut

changes in the ballistocardiogram serves only to emphasize the already recognized differences in behavior between cardiac and skeletal muscles in the usual attack of periodic paralysis. No clinical signs of alteration in cardiac action were found during the episode of paralysis studied.

SUMMARY

1. A single spontaneous episode of periodic paralysis is shown to have been preceded for six days by a gradually falling output of both urine and potassium without change in the serum potassium level until the latter fell precipitously on the day of paralysis.

2. Serum and muscle analyses during paralysis revealed a marked increase in extracellular and intracellular water, a marked increase in the absolute amount of intracellular potassium referred to muscle solid which was due in large part to a shift from nonmuscle tissues, and an increase in the ratio of concentrations of intracellular to extracellular potassium due largely to the fall in the extracellular level of potassium.

3. Reference is made to experimental observations which suggest the hypothesis that the paralysis of striated muscle in our subject was related to an increase in the resting membrane potential, which in turn was determined by the increase in the ratio of the concentrations of intracellular to extracellular potassium.

The serum and muscle analyses were performed in the research laboratory of the department of medicine, Medical College of Virginia, Richmond, under the direction of Dr. Reno R. Porter, for whose generous help we are very grateful. For the urine potassium determinations we are indebted to the Second Army Area Laboratory, Ft. Meade, Maryland.

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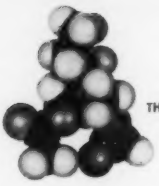

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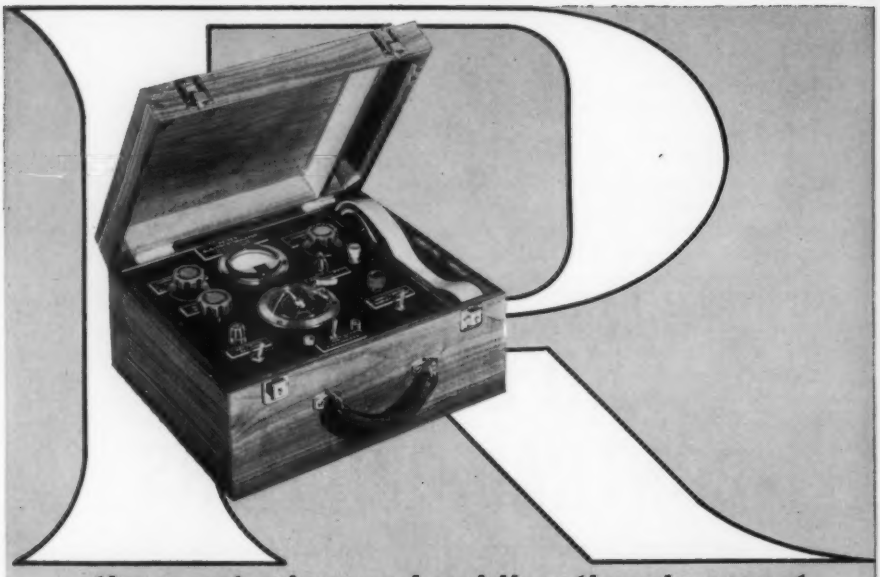

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1. Fazekas, J.F., et al.: J.A.M.A. **161**:46 (May 5) 1956. 2. Mitchell, E.H.: J.A.M.A. **161**:44 (May 5) 1956.

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JULY, 1956

1957 AAN Meeting To Be Held In Boston The ninth annual meeting of the American Academy of Neurology will be held at the Sheraton-Plaza Hotel in Boston (April 22-27, 1957). Preliminary planning for the meeting has been started by general program chairman and coordinator Frederick L. Stone, scientific sub-committee chairman James L. O'Leary, and local arrangements chairman Joseph M. Foley.... As is customary, the scientific sessions will be preceded by committee meetings and the AAN special review courses. The courses in neuropathology (Fae Y. Tichy), neurochemistry (Donald B. Tower), and current advances in neurology (Joe R. Brown) will be given again. In addition, there will be new courses on episodic diseases of the nervous system (Francis M. Forster), the brain and its communication systems (Gilbert H. Glaser), pain and pain pathways (Charles A. Kane), and neuroroentgenology (A. L. Sahs). All communications relative to these special courses should be sent to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minn.

AAN Membership Expands The AAN campaign to expand its present membership in all categories, particularly the number of its associate members, has resulted in the addition of 46 new members during the month of May. These new members (all categories) are: Leon L. Bernstein, (Youngstown); Carmine D. Clemente, (Los Angeles); Douglas T. Davidson, Jr., (Boston); Raymond Dawson, (Richmond); Eric Denhoff, (Providence, R.I.); Harold Dinken, (Denver); J. G. Frontera, (San Juan, P.R.); William J. Fry, (Urbana); Russell V. Fuldner, (New Haven); George D. Gammon, (Philadelphia); Lois A. Gillilan, (Philadelphia); David Grob, (Baltimore); Ward C. Halstead, (Chicago); Albert Heyman, (Durham); John R. Hughes, (Bethesda); Tryphena Humphrey, (Pittsburgh); Robert N. Hollenhorst, (Mayo Clinic); Peter Kellaway, (Houston); Margaret A. Kennard, (Fort Steilacoom, Wash.); Charles Kennedy, (Philadelphia); Robert A. Knight, (Memphis); Ruth Krauss, (Buffalo); Charles N. Luttrell, (Baltimore); John W. Magladery, (Baltimore); C. C. McClure, (Nashville); Donald S. Miller (Chicago); George S. Morrison, (Roswell, N. Mex.); Kermit E. Osserman, (New York); C. M. Pomerat, (Galveston); Lt. Thomas J. Preziosi, (Bethesda); Maria Isabel Robert de Ramirez de Arellano, (Santurce, P.R.); James J.

Ryan, (Philadelphia); Harold F. Schuknecht, (Detroit); Charles D. Shields, (Washington, D. C.); Fred M. Taylor, (Houston); Robert D. Teasdall, (Baltimore); J. Edward Tether, (Indianapolis); Oscar A. Turner, (Youngstown); Ludwig von Sallmann, (Bethesda); Jean Kendrick Weston, (Detroit); William C. Wilson, (Elgin); Charles S. Wise, (Washington, D. C.); Stewart Wolf, (Oklahoma City); Clinton N. Woolsey, (Madison); S. Bernard Wortis, (New York); Harry M. Zimmerman, (New York)....Fellowship and active membership in the Academy are open to diplomates in neurology of the American Board of Psychiatry and Neurology, or to those certified in neurology by the Royal College of Physicians and Surgeons of Canada, who have been sponsored by two fellows or active members of the AAN. Junior membership is open to graduates of class A medical schools, who are in residency training in neurology. Eligible for associate membership are those in advanced training in clinical neurology, and physicians in other clinical fields or neurologic scientists who have made a contribution to the advancement of our knowledge of the nervous system....Candidates for active membership, with the proper sponsorship, should apply to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minn. Candidates for associate membership should apply to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

Conference on Brain Damage To Be Held in Puerto Rico

The School of Medicine of the University of Puerto Rico, in conjunction with United Cerebral Palsy Association, the National Multiple Sclerosis Society, Association for the Aid of Crippled Children, and the National Institute of Neurological Diseases and Blindness, will sponsor a conference on "Asphyxia Neonatorum, Brain Damage and Impairment of Learning in Experimental Animals" (August 29-September 1, 1956). The conference will be held at the Medical School of the University of Puerto Rico at San Juan, and will bring together leading investigators who are currently engaged in research on experimental cerebral palsy and mental retardation. It is timed to coincide with the initiation of a cooperative field research project between the Medical School of the University of Puerto Rico and the NINDB's Laboratory of Neuroanatomical Sciences, under William F. Windle. The purpose of the cooperative project is to investigate casual relations of certain factors, including neonatal asphyxia, during the perinatal period which resulted in brain damage and neurologic deficits. These investigations, which will be carried out on a free range colony of rhesus monkeys on the offshore Puerto Rican Island of Cayo Santiago, will be a part of the NINDB's total program of field investigations in cerebral palsy and mental retardation (see May 1955 Newsletter)....The conference will be opened with a dinner meet-

ing the evening of August 29 at the Caribe-Hilton Hotel, followed by scientific presentations and discussions, and concluded with a symposium on "Breeding and Care of Monkeys for Scientific Purposes."

Joint Meeting on Cerebral Vascular Disease

On May 24 at the National Institutes of Health in Bethesda, there was a joint meeting of selected members of the National Advisory Neurological Diseases and Blindness Council (H. Houston Merritt and David G. Cogan) of the National Advisory Heart Council, and (Irving S. Wright and Irvine Page) with Dr. Wright serving as chairman. The purpose of the meeting was to implement the national research effort in cerebral vascular disease and to explore new avenues of research. The committee agreed that the problem of cerebral vascular disease is a major one, indicating that mortality statistics show that 25 per cent of all cases coming to autopsy have cerebral vascular lesions and the estimated morbidity figures in the U. S. are approximately 1,800,000....The committee also emphasized the vital need for clinical research in this area, as well as increasing emphasis on basic research and encouragement of young clinicians and scientists to enter this field. The final recommendation of the committee was toward the establishment of an inter-Council committee (Neurology and Blindness and Heart) to stimulate research in these problems and make recommendations to all the National Advisory Councils of the National Institutes of Health ....An important correlate to the inter-Council meeting is the announcement of a second conference on cerebral vascular disease, sponsored by the American Heart Association, to be held at the Nassau Tavern, Princeton, N. J. (Jan. 16-18, 1957).

* * * * * *

Canadian Neurological Meets in Quebec

The eighth annual meeting of the Canadian Neurological Society was held in Quebec City (June 7-9). The program consisted of presentation of scientific papers at the Quebec Winter Club by leading Canadian neurologists and visitors from abroad, a symposium on Undergraduate Neurological Education under the chairmanship of Francis L. McNaughton, and a lively program of social activities and excursions for which Quebec is so renowned. Included in these activities was an Open House in the home of President Jean Sirois, a reception at the Manoir Saint-Castin, Lake Beauport, and the annual dinner of the society which was held at the Chateau-Frontenac. A guest of honor was Prof. Raymond Garcin, French vice-president to the International Congress of Neurological Sciences, who spoke on hemiballismus and purpura. Among the AAN members who presented scientific papers were G. Milton Shy and J. Lawrence Pool.

Carmichael Visits the U. S. Dr. E. Arnold Carmichael, director of the medical research unit of the National Hospital, Queen Square, London, in company with Dr. B. Lush of the Medical Research Council's administrative staff in London, visited several institutions in the U. S. to discuss human factors in military operations other than those in the strictly medical field. Despite many pressing obligations when in Washington, Dr. Carmichael, who has many former students in this country, visited the National Institute of Neurological Diseases and Blindness, together with Dr. Lush and Surgeon Commander F. P. Ellis of the British Royal Navy. After looking at the NINDB laboratories and adding light to a weighty diagnostic problem, Dr. Carmichael returned to the more general duties of his mission. Before returning to England, he attended the American Neurological Association meeting in Atlantic City.

Briefs After 36 years of service, Frederick P. Moersch, senior neurologic consultant at the Mayo Clinic and professor of neurology at the University of Minnesota Graduate School, retired on April 1. Among the many important appointments held by Dr. Moersch were the presidency of the American Board of Psychiatry and Neurology in 1955, secretary of the Section on Nervous and Mental Diseases of the American Medical Association (1947-50), and chairman of the section in 1951....Under the sponsorship of the Muscular Dystrophy Associations of America, a muscular dystrophy clinic has been established at the Hospital for Crippled Children, 89 Park Avenue, Newark, N. J. Patients may be referred by private physicians or other clinics....The Sixth Neuroradiologic Symposium will meet with the First International Congress of Neurological Sciences, to be held in Brussels (July 21-28, 1957). President of the symposium is Dr. L. McRea of Montreal; the Secretary General, Prof. G. J. Melot, 120 Avenue de la Tolson d'Or, Brussels, Belgium....At a luncheon at New York's Ambassador Hotel (May 23), the Albert Lasker Awards for outstanding reporting on medical research and public health in 1955 were made to Selig Greenberg (Providence, R. I. Journal and Evening Bulletin), for "Hormones: Revolution in Medicine"; Mrs. Joan Geyer (Provo, Utah, Daily Herald), for "The Secret Sickness—Mental Illness"; Steven M. Spencer (The Saturday Evening Post), for "Mystery of the Blinded Babies" (retrolental fibroplasia); and to the Smith, Kline & French Laboratories, for their television series, "The March of Medicine."....Herman Holland DeJong, AAN member and director of research and education at the Osawatomie State Hospital in Kansas, died on Feb. 16....

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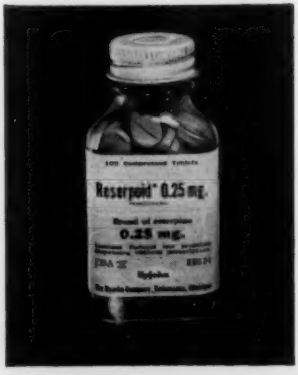

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(1) Rodriguez-Gomez, M., Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. *160*:752 (Mar. 3) 1956. (2) Amols, W.: J.A.M.A. *160*:742 (Mar. 3) 1956. (3) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. *160*:749 (Mar. 3) 1956. (4) Smith, R. T.; Kron, K. N.; Peak, W. P., and Hermann, I. F.: J.A.M.A. *160*:745 (Mar. 3) 1956.

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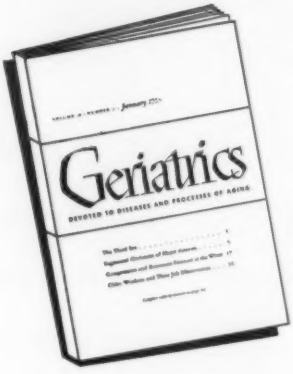

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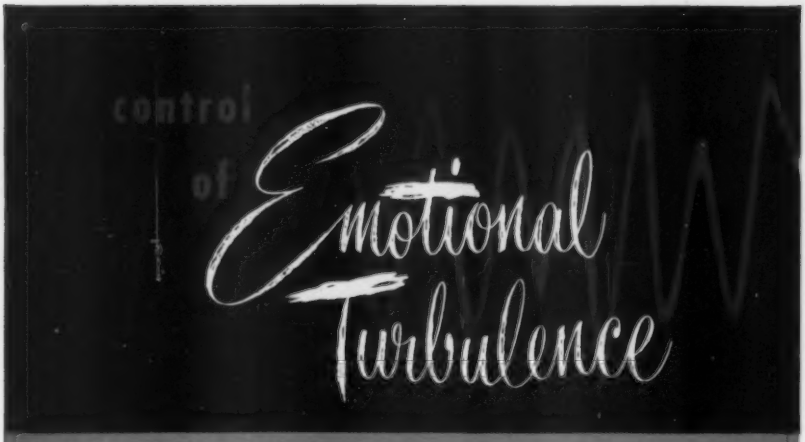

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